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DIABETES MELLITUS

Handbook for Physicians

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PREFACE

This handbook is intended primarily for the day to day use of the physician in practice and is devoted to the management of diabetes and its complications The relation of diabetes mellitus and general medicine, including obstetrics, pediatrics and surgery, is presented Complications or sequellae of diabetes, including cardio-vascular, renal, pulmonary and ocular disorders associated with diabetes or consequent upon imperfect control of diabetes have been emphasized Attention has been given to the basic concepts of diabetes and particularly to the long range objectives of treatment since today it is becoming more evident that these objectives must be kept clearly in mind and treatment planned for many years The importance of adequate, careful control of diabetes from the very outset of the disease and the continuing education of the patient have become more and more evident

Treatment by means of diet and insulin, including reference to the recent development of oral treatment have been described as they have been generally employed at the New England Deaconess Hospital and in office practice at the Joslin Clinic, Boston We have sought to select topics which illustrate the difficulties of treatment encountered in the management of patients

We are indebted to all our patients and their doctors to whom we owe the experience in the treatment of diabetes, upon which this book is based Especially to Drs Elliott P Joslin, Alexander Marble, Allen P Joslin, Robert

F Bradley and Leo P Krall, we are grateful for stimulating aid References to medical literature are few in this text, but we would here express our gratitude to the many students of diabetes and of carbohydrate metabolism, whose work has made possible our present understanding of diabetes

HOWARD F ROOT
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June, 1956
Boston, Mass

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DIABETES MELLITUS

CHAPTER I

NATURE OF DIABETES

Definition Diabetes mellitus is a chronic, hereditary disease characterized by persistent hyperglycemia and glycosuria Its major clinical manifestations are due to deficiency of insulin which may be the result of such causes as, (1) faulty production of insulin by an abnormal pancreatic islet mechanism, (2) to increased destruction of insulin by specific or non specific proteinases, (3) to faulty utilization of insulin due to inhibiting agents of unknown nature and (4) to an increased tissue requirement for insulin in order to maintain normal carbohydrate metabolism According to present concepts the inherited tendency to diabetes is transmitted as a simple mendelian recessive trait It is this hereditary character of true diabetes mellitus which distinguishes it from temporary or transitory hyperglycemic states The action of insulin in the body affects not merely carbohydrate, but also protein and fat metabolism As the duration of diabetes has increased with the improvement in the use of diet and insulin, features of diabetes not previously recognized have become apparent Today the sequelae or complications of diabetes involve not only all elements in the vascular system, from capillaries and venules of the retina to the largest arteries, but also the endocrine system and the central nervous system The objectives in the treatment of diabetes must be broad indeed and, therefore, include the improvement of the patients present and future state and the future of his entire family

The Pancreas The endocrine function of the

was demonstrated when Minkowsky and von Mering produced diabetes by pancreatectomy in a dog in 1886 The isolation of insulin from the pancreas by Banting and Best occurred 35 years later The endocrine glands serve as regulators or integrators of functions which are characteristic of tissue cells The level of integration of hormonal activity in the body depends upon genetic factors which affect growth and development As study has progressed, insulin appears to be a hormone of extraordinary anabolic capacity

The pancreas develops from two buds, one from the dorsal wall of the duodenum and the other from the hepatic diverticulum The dorsal pancreas connects with the duodenum by the duct of Wirsung Fusion of these two primordia during intrauterine life leads to the formation of the structures of head, body and tail The fetal pancreas has little or no exocrine function and the pancreas of the infant of the diabetic mother consists almost exclusively of beta cells

The endocrine islets of Langerhans make up 1 0 per cent of the weight of the pancreas They are scattered throughout the pancreas, numbering approximately 2,000,000 These islets vary in diameter from 20 to 300 micra Rich capillary blood supplies are surrounded by distinct types of cells, the alpha cells and the beta cells The latter cells contain granules during the inactive secretory phase which are pretty definitely known to be insulin The finer granules in the alpha cells are presumed to be glucagon, the hyperglycemic factor of the pancreas Non granulated C cells have been described

Pathologic findings in the islets have correlated fairly well with determinations of the insulin content of the pancreas but not so well with various degrees of clinical diabetes A pathologic change in the islets has been present in from two thirds to three-fourths of all patients with diabetes The changes consist of hyalinization of the islets, fibrosis chiefly. Hydropic degeneration represents glycogen deposition in

the beta cells Lymphocytic infiltration is rare and is chiefly found in children or young patients

Clinical Diabetes

Incidence Due to the relatively high incidence of the disease in all societies, to the long period of medical supervision required and to the disabling sequellae and complications which occur with increasing frequency in later life as the duration of the disease continues, diabetes has become a disease of increasing importance both from medical and social viewpoints

In the United States approximately 1,000,000 persons with diabetes may be expected to live from 12 to 25 years with the disease It has been estimated that 4,000,000 individuals now alive in the United States will develop diabetes before death Increasing mortality rates have occurred since the turn of the century In some states diabetes has caused more deaths than tuberculosis

Sex After the fourth decade the incidence of diabetes among females is greater than among males After fifty years of age the mortality rate for women is practically double that for men and higher in married women than in single ones

Race For many years the incidence of diabetes has been regarded as greater among Jews than in other races However, if allowance be made for inter-marriage and the increasing influence of heredity it is possible that no greater incidence in the Jewish race exists than in other races

Heredity For many years students of diabetes have suspected that the inheritance of a predisposition to diabetes followed a genetic pattern In recent years, however, careful studies have left no doubt that heredity is a real factor! Careful studies of large groups of patients would indicate that the excess of diabetics had close relatives who were patients In similar twins high coincidence of diabetes known

Obesity bears a close relationship to the incidence of diabetes, particularly in middle and late years This is more marked among Jewish patients The exact nature of relationship in obesity and diabetes is still under investigation

Hormonal factors undoubtedly play a part in etiology Hormones, other than insulin, may exert an antagonistic effect on carbohydrate metabolism This may occur by decreasing the secretion of insulin, by inhibiting its action, or by creating a heightened level of metabolic activity which requires more insulin

Diagnosis The striking symptoms of diabetes include loss of weight and strength in spite of an adequate or excessive intake of food, polyuria, polydipsia, pruritus, blurred vision, a variety of cramping or lightning pains and a family history of diabetes Physical findings suggestive of diabetes include skin infections, notably carbuncle, xanthochromia and premature vascular changes in legs, coronary vessels and retinae In the presence of such symptoms diagnosis may be made without clinical tests When necessary, however, the diagnosis should always be established in any person suspected of true diabetes mellitus by chemical examination of the blood and urine Many patients, especially adults, may have diabetes mellitus with glucose in the urine and blood sugar levels above normal for months or even years without recognizing any of the above classical symptoms Indeed, today's problem is the recognition of patients with early diabetes or even incipient or latent diabetes before any of the classical symptoms have developed in order that by earlier institution of treatment many later complications in the vascular system, central nervous system and endocrine system may be postponed or entirely prevented In children, true diabetes mellitus seldom exists for many weeks or months without symptoms which lead the parent to seek medical advice Indeed, in infants the progression of the disease is so rapid that ordinarily ketoacidosis is pres

ent as the presenting symptom in most cases The diagnosis of diabetes mellitus, therefore, should be made early and should be based on adequate blood and urine tests

Criteria for Diagnosis The requirements for a diagnosis of diabetes mellitus are (1) glycosuria, (2) fasting or postprandial hyperglycemia, and (3) a diabetic type of glucose tolerance curve Normally, the level of glucose in the blood in the fasting state varies from 70 mg to 120 mg per 100 cc when determined by the Folin Wu method in venous blood Following a meal containing carbohydrate in liberal amounts, the level of glucose in the venous blood will be found to rise rapidly during the next 45-60 minutes to a level which should not exceed 160 mg, and the blood sugar should return to the normal fasting level at the end of two hours after a meal When capillary blood is used for the determination, the values are correspondingly higher since the capillary blood is essentially arterial blood Thus, the capillary blood sugar level an hour after a meal containing carbohydrate, or after a glucose tolerance test, may reach a level of 190 mg or even more with levels fasting and 2-3 hours after the meal of 100-140 grams of carbohydrate

True glucose values in the blood (Somogyi Nelson) usually are 20-30 mg lower than values obtained by the Folin Wu methods

Normally, no glucose appears in the urine except under conditions of stress as in fever, excessive intake during and following the intravenous administration of glucose, or in conditions which affect carbohydrate metabolism such as hyperthyroidism, toxemia, anesthesia, rheumatoid arthritis Under these circumstances the amounts are usually small and temporary When glucose appears in the urine following the ingestion of carbohydrate meals and disappears or its concentration markedly reduced by reducing the carbohydrate in the diet, a strong suspicion of diabetes s exist

Other types of melituria include lactosuria, galactosuria, pentosuria and levulosuria, as well as sucrosuria (see page 323)

The presence of both glycosuria and ketonuria, indicated by strongly positive tests for acetone and diacetic acid, usually indicates diabetes mellitus A reduction in the carbon dioxide combining power and increased blood lipids (notably a cream plasma) are signs of complications indicating a more severe stage of the disease

Glycosuria may be discovered by any of the standard methods, based on the capacity of glucose to reduce alkaline copper solutions, such as Benedict's solution In normal urine, the concentration of reducing substances is too low to give a positive test Commercial tablets containing necessary reagents are available

Reducing substances in the urine need not be glucose Salicylates, camphor, chloral hydrate and morphine may result in excretion of reducing substances

True glycosuria with normal blood sugars may occur as a result of activity of the glands of internal secretion other than the pancreas, as in hyperthyroidism, in hyperpituitarism and in conditions where overactivity of the suprarenal glands occur Other causes of glycosuria with normal blood sugar are stimulation of intracranial nerve centers, as in brain tumors, cerebral hemorrhage or injury to the skull, alimentary glycosuria, degenerative conditions such as vascular hypertension, chronic nephritis, malignant disease, and finally chemical agents such as phloridzin, poisoning with curare, carbon monoxide, chromium salts, and bichloride of mercury

The finding of glucose in the urine at any time should be considered as indicative of diabetes until the contrary is proven During the course of infection after periods of inactivity, after periods of stress and particularly after or during certain complications, glycosuria may appear indicating

that under stress a person with truly genuine diabetes has been found Such findings should always be confirmed by a test of the blood sugar, even one hour after a meal or by the administration of a glucose tolerance test The experience of many careful workers has shown that it is unwise to neglect the finding of so called "traces" of sugar in the urine, or the green reduction with a copper solution such as Benedict's Many such patients when subsequently subjected to a careful glucose tolerance test will be found to have diabetes mellitus A new concept introduced by students of genetics suggests that there may be some patients who are carriers of the diabetes tendency who will show occasional hyperglycemia either fasting or after glucose without other evidences of diabetes who may be heterozygotes and are, therefore, unable to develop clinical diabetes This subject is under intensive investigation at the present time It follows that the occurrence of glycosuria under any circumstances is deserving of attention and careful investigation

Tolerance Tests Since in the diabetic patient the fasting blood sugar may be at times normal, various food and sugar tolerance tests have been devised in the attempt to identify the patient as a true diabetic or as a non-diabetic Such tests may often be fallacious or at least difficult to interpret The previous diet of the patient, the presence of mild infections or other factors may affect results Every meal containing a moderate amount of carbohydrate is in a sense a tolerance test In general, therefore, the practice of testing the blood and urine an hour after a meal containing 100 grams of carbohydrate or more will frequently discover a hidden diabetic patient

(a) *Food Tolerance Test* A breakfast containing roughly 100 grams of carbohydrate in the form of orange juice, a cup of cereal, a glass of milk, 2 slices of bread and jelly may be eaten and the blood sugar and urine tested one hour

later If at this time glycosuria and the blood sugar level exceeding 170 mg, venous blood, are obtained, presumptive diagnosis of diabetes may be made

(b) *Glucose Tolerance Tests* Such tests are carried out by determining the blood sugar level and the glycosuria present at stated intervals following the taking of a standard amount of glucose orally or intravenously A standard glucose tolerance test consists of taking 100 grams of glucose or 1 75 grams of glucose per kilogram of body weight by mouth In children, the common practice is to give 1 gram per pound of body weight up to a weight of 100 pounds The glucose solution is flavored with lemon juice The blood sugar is determined prior to the taking of glucose and then at ½, 1 hour, 2 hours and sometimes 3 hours later The finding of glycosuria and a blood sugar level exceeding 170 mg, either at the peak of the curve at 1 hour or failure of return of the blood sugar to normal at the end of 2 hours, is presumptive evidence of diabetes A flat glucose tolerance curve may indicate failure to absorb glucose at a normal rate due to pyloric spasm or some gastrointestinal disorder

The one hour, two dose, oral glucose tolerance test (Exton Rose Test) depends upon the failure of a moderate amount of glucose to raise the blood sugar of a normal subject if this dose is administered within an hour after giving a primary dose of glucose previously The method consists of taking 50 grams of glucose in 400 cc of lemon flavored water (fasting) and measuring the venous blood for blood sugar at the end of ½ hour Then, another 50 grams of glucose is administered and ½ hour after that a second blood sugar sample and urine test is made Normally, the fasting blood sugar will be below 130 mg per 100 cc of blood, the ½ hour level should not exceed 170 mg per 100 cc of blood and at 1 hour the level should be below the ½ hour value

Intravenous Glucose Tolerance Tests Glucose is administered intravenously at a rate of 0 5 gm per kilogram per ½ hour The blood sugar is determined in the fasting state and again at 30, 60, 90, 120 and 180 minutes following the beginning of the injection Normal values should be attained at the end of 90 minutes

A fourth method intended to discover diabetes in a very early stage depends upon the administration of cortisone as a test substance and then use the glucose tolerance test thereafter This test is still under investigation

The standard glucose tolerance test of 100 gm of glucose, is the one most commonly used A large mass of clinical experience with this test is available for comparison This test, however, is difficult to interpret if it is carried out under circumstances which have not been standardized Thus a glucose tolerance test carried out in the presence of infection or fever or previous severe dietary restriction or the previous administration of insulin will be impossible to interpret Therefore, patients should certainly have received a diet containing at least 200 grams of carbohydrate for 3 days preceding the day of the test and should have had no insulin for a corresponding period No food should be taken for at least 12 hours before the beginning of the test It is our practice to take the patient s temperature at the beginning of the test and at the end merely to rule out the possibility that a beginning infection may be present

The use of blood sugar methods which determine true glucose (Somogyi Nelson) in contrast to the Folin-Wu or Benedict methods should before long find general acceptance throughout the clinical laboratories in the country If such a method is used, the diagnostic levels for venous blood are fasting 110 mg per 100 cc, peak 50 mg per 100 cc and the 2 hour value, 100 mg per 100 cc It has been our practice to use both the Folin Wu and the Somogyi-Nelson method, but until there is more general acceptance

of the true glucose methods the older techniques are more generally understood, and the interpretation may be more generally accepted

Classification of Patients with Suspected Diabetes

In any group of patients who are found on casual examinations to have glycosuria without the classical symptoms and signs of diabetes mellitus, it will be found helpful to have some sort of classification based upon blood and urine tests The following classification has been found practical and acceptable over the years

1 *Diabetes Mellitus*—Glycosuria and hyperglycemia in a glucose tolerance test or after a meal as previously described
2 *Renal Glycosuria*—This title is given to the condition in which patients show glucose in the urine at all times regardless of the level of blood sugar and blood sugar levels are constantly normal Such patients do not have any of the symptoms of diabetes, but they frequently are members of families in which diabetes or other types of glycosuria have been found This condition may be found early in life and has been observed throughout life without any tendency to advance to a true diabetic state By definition renal glycosuria implies that the renal threshold is so low that even after fasting and a fall of blood sugar level to 80 mg or less there will still be glycosuria A typical glucose tolerance curve for a case of renal glycosuria follows

	Fasting	*30 minutes*	*1 hour*	*2 hours*
Blood Sugar	110 mg	132 mg	130 mg	120 mg
Urine Sugar	1 5%	2 0%	2 2%	1 8%

It seems at present likely that the glycosuria depends upon the incomplete reabsorption of glucose from the renal

tubes and this deviation may be due to a deficiency in tissue phosphatase

3 *Potential Diabetes*—This classification was given to patients in whom glycosuria has been found which disappears on restriction of diet and yet no other classical symptoms of diabetes are present Frequently, the patient has a known family history of diabetes A typical glucose tolerance curve follows

	Fasting	*30 minutes*	*1 hour*	*2 hours*
Blood Sugar	110 mg	155 mg	162 mg	120 mg
Urine Sugar	0%	0 1%	0 3%	0%

In this group the fasting blood sugar may be normal, but the blood sugar rises to perhaps 160 mg with or without slight glycosuria and returns to normal at the end of two hours In this group might be included, also, some patients with occasional hyperglycemia, for example, the blood sugar of 180 or 190 mg without sugar in the urine who upon ordinary diet without excess carbohydrate content will be continually sugar free and show usually normal blood sugar values The frequency of a family background in this group and the fact that when followed over a period of years, roughly 10 12 per cent of these patients do develop true clinical diabetes mellitus, makes this group one of special importance to the physician

4 *Unclassified Glycosuria*—This classification includes all other cases with occasional glycosuria without hyperglycemia in whom such factors as drug administration, a slight infection, and the effect of other stresses cannot be entirely quantitated or determined Many causes, such as disorders of other glands of internal secretion, namely, thyroid, pituitary, and adrenal, stimulation of intracranial nerve centers, alimentary, or febrile influences or degenerative conditions chemical agents may play a part in this group

It is important to remember that when glycosuria persists in spite of change in diet and when blood sugar tests have been normal, other melliturias such as pentosuria, levulosuria, lactosuria, galactosuria should be sought The actual technical methods are given on page 323 Galactosuria is a rare but important metabolic disturbance frequently associated with formation of cataracts and frequently with mental retardation, for which treatment depends upon the elimination *of galactose from the diet Pentosuria is a rare metabolic disorder found in a limited number of Jewish families,* but quite harmless Fructosuria may occur with diabetes and it is true that some diabetic patients with large amounts of glucose in the urine will also show fructose However, as a separate entity, fructosuria is a rare phenomenon, quite *harmless and requiring no dietary treatment*

Examination of the Patient In no chronic disease is repeated examination of patients at regular intervals of greater importance than in the treatment of diabetes This statement is based upon the experience of many years which has indicated on many occasions how easy it is to miss the early signs of serious diabetic complications *on the one* hand, or by failure to examine the patient carefully and to overlook the early signs of serious complications unrelated to the diabetes The diabetic patient, as the years go by, affords the physician a repeated opportunity to practice preventive as well as therapeutic medicine By taking ad vantage of the frequency of office visits, *he will discover in* its incipiency many of the complications in a stage where successful therapy will prevent serious and long disabling illness

First Examination of the Diabetic The presenting complaint of the patient may be misleading Diabetes in an uncontrolled state can *lead to symptoms in any of the major systems of the body During hyperglycemia,* changes in vision are frequent and severe though, fortunately, often of temporary character Marked dizziness frequently occurs



TABLE 1—Continued

Location of Lesions	*Early Cases*	*Diabetes of Long Duration*
Extremities	Edema in Neuropathy	Absent pulsations in feet numbness anesthesia of feet or fingers
Urinalysis	Sugar diacetic acid and acetone in acidosis	Albuminuria glycosuria

Examination of the patient should always include a consideration of his own emotional state Often in early cases, particularly in young adults, the shock of discovering an illness which is bound to be chronic is associated with real depression and anxiety, which may last for a long time Such patients sometimes feel themselves hopelessly set apart from their fellows or hopelessly handicapped and without chance for a good future Reassurance may come as they find themselves able to control the manifestations of diabetes in the urine and blood The great advantage of urine and blood tests is not only their value to the doctor in directing treatment, but the reassurance which is given to the patient that he has objective evidence of his own ability to control the disorder

Actually, the physician who sees many patients with dia betes, particularly those of the more severe type and those with labile diabetes, becomes accustomed to asking himself with every patient, "Is this person near hypoglycemia from insulin and over exercise, or is he near true acidosis and diabetic coma?' Every physician knows that diabetic patients, while considered chronic and often unchanging nevertheless do change rapidly either under the influence of insulin or more particularly, under the influence of insulin deficiency The development of acidosis and diabetic coma is most insidious Changes in the bowel movements, abdominal pain or particularly the influence of fever, in fection or other complications, may be followed within a few hours by acidosis and all the dangers incidental to severe diabetic ketosis Once the patient has had a severe

diabetic decompensation with acidosis or coma, the diabetes may become progressively more severe In addition, however, complications notably in the eyes and kidneys develop with much greater frequency in such patients Within the next 3 5 years pulmonary tuberculosis is a frequent sequel of severe diabetic coma *It is advantageous, therefore, to* have physical examinations at intervals in the physician's office, but x ray examinations of the chest once a year as well The early development of pulmonary tuberculosis and its discovery in a favorable stage can yield even better results than a similar lesion in the non-diabetic This is particularly true if one can, by means of insulin, restore metabolic conditions to a more nearly normal level when the previous severe decompensations of diabetes has been itself a major factor in favoring the development of active tuberculosis

CHAPTER II

TREATMENT WITH DIET

General Considerations

The objectives in the management of the diabetic patient may be summarized as follows

(1) Correction of the disordered metabolism by means of insulin, dietary adjustment or both
(2) The attainment and maintenance of normal nutrition with body weight approaching the ideal for age, height and sex
(3) Preservation of the remaining insulin producing power of the pancreas
(4) The prevention, postponement or treatment of complications and sequelae of the disease

The relief of acute symptoms, such as nocturia, polyuria, blurred vision or ketosis is promptly and easily accomplished, often by insulin alone Without dietary adjustment, it is difficult to avoid insulin overdosage or glycosuria Without proper dietary treatment obesity develops easily Freedom from symptoms is not a safe or sufficient objective alone Maintenance of body weight close to the ideal can be accomplished in most patients The incidence of complications increases with either obesity or undernutrition Most of the severe complications, notably retinitis, nephropathy, neuropathy and ketosis can be prevented by early and continued use of insulin, diet and adequate control of the disease

The first step in diabetic care is the doctor's willingness and ability to meet the challenge presented by the patient's need for treatment He must then not only regulate the patient's diabetes and teach methods of maintaining this regulation, but also he must sense the very real fears of the diabetic concerning the impending changes in his daily routine and what appears to be uncertain future At this point all the long range objectives may either "sink or swim" The physician's support is vital

Reassurance represents an important bulwark of this support, but only when tempered with simple, carefully taught facts about diabetes is it effective As the patient learns, correction of the physiologic disturbance should be underway Usually symptoms will improve, a sense of well being is noted and confidence begins At first, confidence is shared wholly or in part with the doctor Ideally, this assurance over days, weeks, or months depending upon the individual patient reaches that stage wherein the diabetic can handle his disease under any daily condition except for acute illness or some unusual event Later, no matter how intelligently and carefully the confident patient may believe he is handling his diabetes, and regardless of how well he may feel, he will require periodic supervision by his physician preferably at intervals of one to four months At these times effectiveness of the diabetic program should be evaluated by (1) freedom from symptoms of diabetes, (2) eliciting from the patient the nature of the food and their amounts *actually eaten*, (3) results of urine tests for sugar at home, (4) *estimations of blood sugar and glycosuria*, (5) necessary changes in the diet and insulin prescriptions and (6) continuation of diabetic education and reaffirmation of the cardinal principles in day to day care Here the physician has his best opportunity firmly, but sympathetically to emphasize the role of diabetic control in preventing or measurably delaying complications

Methods of Treatment

None of the major tools in the treatment of diabetes can alone be successful, but together their intelligent and continued use will allow the objectives to be reached

(*a*) *Education* This is acquired by the patient from

(1) *The Doctor* There is no substitute for what he can teach, because his words carry authority and will be best remembered An attitude of pessimism is often damaging Rather, he should give reassurance that (a) diabetic symptoms will be relieved, (b) daily activity and occupation need not be curtailed or changed, (c) physical strength and stamina as well as mental capacity will be retained, (d) a diabetic diet today is not one of starvation, (e) in most instances a normal expectancy of life may be anticipated, (f) infections, injuries, and surgical operations may be well tolerated, and (g) for women, pregnancy is without great risk and with adequate care is usually successful

The respect and cooperation of the diabetic cannot be gained when the physician is unable himself to prepare a diabetic diet, make accurate changes in it, or does not have a working knowledge of the basic elements in commonly used foods It would be well for the doctor to calculate his own food intake in carbohydrate, protein, fat and calories He should certainly not prescribe a diet he would himself be unable to follow, nor should he expect his patient to know facts about diabetes with which he is not familiar

(2) *A Well-Trained Dietitian* The details of diet and preparation of pleasing menus as well as the time consuming teaching of techniques for urine testing and insulin administration can be well handled by a nurse or dietitian trained for this purpose Much of the doctor's time is thus saved for handling individual problems

(3) *Reading* An accurate, clearly written diabetic manual is of great help for reference and guidance In such a book-

let complete tables of food values should be available *

The ADA Forecast is a readily available pamphlet published by the American Diabetes Association. Its value lies in keeping patients abreast of advances in treatment and reviewing in simple language many basic principles in diabetic care

(4) *Hospital Teaching* Whenever possible, treatment should be initiated in the hospital on an ambulatory basis This is of particular value where nurses, dietitians and physicians have a regular experience in handling diabetic problems Such an approach allows the patient to learn by observation the measurement of food, the distribution and variation in meals, techniques of urine testing and insulin administration.

Opportunities for group psychotherapy are great. The newly discovered diabetic often is encouraged when he finds that diabetes is a common disease and how well others may be after many years Where larger numbers of diabetic patients are available, informal lectures may be given daily and are of considerable help in improving mental outlook as well as disseminating simple facts about diabetes and related subjects to many patients and their relatives

Again a hospital stay of 4-5 days may be advised after one two, or three years to readjust the diet and insulin program, but even more important it should serve to reaffirm principles of treatment forgotten or confused by the passage of time

(*b*) *Diet*

The principles of the diabetic diet are simple, but ,' of its administration often pose difficulties Today the poses of dietary treatment are simply those of diabetic ment as a whole It is one integral part of the four facets in therapy and must always be regulated w consideration for each of the , the

* *Diabetic Manual*, Elliott P Joslin, 9th F

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when first seen, (2) insulin requirement may be dramatically reduced, (3) control of the diabetes is often made easier, and (4) patients usually have an improved sense of well being

The majority of diabetics, excluding those in whom growth is not complete, will do best on 25-30 calories/kilogram of *ideal* body weight for height and age With adults, a weight 5-10% below the standard should be attained gradually, but children may be allowed to stay within plus 10% of the ideal for their age and size Weight reduction in juveniles is dangerous It is better to prevent further gain or keep it at a minimum until increases in size and height warrants the existing weight

Some older patients, especially women, cannot be reduced until intake is limited to 15 calories per kilogram of ideal body weight Such diets may be vitamin-deficient, and supplementary vitamins are best administered

Similarly, underweight patients may be given as much as 35 calories per kilogram of ideal body weight until their weight approaches the standard

There is no absolute rate at which weight should be lost. Two pounds per week is often quoted as safest However, many persons lose in step like fashion, so that it is helpful to set a figure about half way between the current and ideal weights for the patient to reach in 1 year Grossly overweight and otherwise healthy persons may safely accomplish this in 4-6 months

Regular evaluation of physical condition allows (1) reassurance if weight is falling precipitously, based on examination to rule out other lesions that might be contributing to this loss, (2) encouragement in continuing diet restriction when inadequate weight loss is found, (3) explanation of unpleasant symptoms often experienced by obese patients, (4) modification of dietary intake to adjust the rate of fall in weight, and (5) as most frequently is necessary, a careful review of food actually eaten Most patients follow quali

insulin is doing embraces *new facts showing that its powerful* hormonal action is necessary not only in the utilization of carbohydrate, but also in building protein (Lotspeich, *Chaikoff) and forming fat (Stetten)* Most recent evidence even suggests that insulin is a critical factor in the promotion of growth (Best) Thus diabetes mellitus, primarily a disease of insulin deficiency, is accompanied by defects in the metabolism of all three major nutrients It follows that treatment must take this fundamental fact into consideration and that *total calories*—whether of carbohydrate, protein, or fat origin—are to be regulated if diet therapy is to succeed

The needs of the diabetic for food are identical with those of the normal person They are conditioned by the same factors—age, sex, body weight, occupation, rate of growth and development and exercise Some workers feel that diabetics may require larger amounts of certain vitamins, *particularly those of the B-complex group,* but this purpose is hardly well served by allowing the patient aimlessly to eat more without supervision

Total Calories

Many estimates of caloric requirements have been taken from figures based on what normal people *eat,* rather than being calculated from their true needs As a result, commonly quoted caloric allowances per kilogram body weight are frequently too high

A statement of the range of caloric intake for most normal adults can be no more than an estimate, but from 1200-3500 calories would be a safe figure

Nearly all authorities agree that obesity should be corrected and in the diabetic everyone would affirm this principle Obviously, to control the weight of diabetic patients, the total intake of food must be restricted Such a program has widespread advantages (1) seventy five per cent of all adult diabetics have been overweight, or are overweight

the permanent diet is a valuable tool in helping to effect rapid control of hyperglycemia and symptoms At times striking remissions may also be produced

Many physicians continue to advocate diets with higher carbohydrate content

(1) Physiologic Plan (Duncan) This allows a nearly normal carbohydrate intake (225 300 gm) and is balanced in total calories by fat restriction (40 75 gm) Tolerance for carbohydrate has made us hesitate to prescribe this much carbohydrate because of difficulty in diabetic control, resulting from increased insulin dosage and wider oscillations in blood sugar levels

(2) Diets containing carbohydrate in the neighborhood of 400 grams per day have few advocates Those who prescribe such diets argue that they prevent ketogenesis, may not increase greatly the insulin requirement because protein consumption is not liberal and fat markedly restricted, and that this amount of carbohydrate more nearly allows a normal diet While it is true that insulin needs may not always be greatly increased there is no proof that such liberal carbohydrate intakes are necessary Furthermore, although many normal young people may customarily take in huge amounts of carbohydrate, it is doubtful that many adults find themselves greatly inconvenienced by keeping *carbohydrate consumption at 200* grams or less per 24 hours At times physicians are asked here to compute their carbohydrate intake and are quite surprised to find how much more carbohydrate must be added for a total of 400 grams to be reached

(3) Free Diets Completely "free diets," i e without any prescription of amounts are without any justification Such dietary programs embrace standards of diabetic control which should appeal only to those physicians desiring to indulge the patients' appetite as well as to avoid expending time in teaching patients, while ignoring late vascular and neuropathic complications Actually, many physicians mean

tative restrictions, but improperly measured or estimated quantities of food may often prevent weight loss Others will occasionally restrict themselves beyond the limits prescribed, which may be particularly dangerous in the diabetic who develops ketosis readily

Seldom will any physician have the good fortune to calculate with perfect accuracy the correct number of total calories at the first visit This is to be expected, and one should always anticipate making periodic revisions It is better to start with a smaller diet than seems indicated an especially useful device when hyperglycemia and glycosuria are pronounced

A maintained reduction in weight will almost invariably improve control of diabetes, reduce insulin requirement, and surely give better opportunity to avoid future complications

Carbohydrate

The normal intake of carbohydrate varies between wide limits—probably 150 400 grams However, the question of *carbohydrate need* is still extensively debated *It is often* stated that carbohydrate should supply 40-50% of total calories Restriction in the diabetic is carried out to make control of the disease easier by minimizing sudden rises in blood sugar and glycosuria Experience with many diabetic patients over a long period indicates that limits of 150-250 grams are effective and safe for diabetics of all ages In *fact, only a small percentage need exceed 200 grams* usually older and growing children, very active young adult males or pregnant women

To avoid ketosis, restriction of carbohydrate should never be below 100 grams and rarely less than 150 grams The only occasion for such marked curtailment is in attempting weight reduction, particularly obese, inactive adult women where fat intake has been maximally reduced without effect

During regulation, lowering of carbohydrate as well as total calories below amounts calculated to be necessary in

ute, it is easier to understand more recent data suggesting that a much higher per cent of protein may ultimately be changed to carbohydrate compounds This may also apply to fat

Adequate protein intake is essential When treatment is first begun, many diabetic patients will acquire a protein deficit During the first few weeks of treatment it may be desirable to give more protein than stated This may be especially important in patients who have had acidosis, great weight loss or during pregnancy and lactation, which rarely occurs The nature of the protein components in the diet are of great importance Thus, protein foods of high biologic value such as meat, milk and milk products and eggs will yield more essential amino acids per gram of protein than will an equal amount of vegetable protein

Dietary protein serves (a) to maintain positive nitrogen balance, (b) to supply sufficient quantities of essential amino acids, (c) as a rich source of vitamins and minerals, (d) to provide many as yet poorly defined constituents useful in intermediary metabolism, and (e) as an excellent means of stabilizing diabetic control because of the slow and continuous manner in which its conversion to carbohydrate may support the level of sugar in the blood

It is striking that both non diabetic and diabetic individuals alike can tolerate increases or great restrictions in dietary protein For example, the rice diet used in the treatment of hypertension allows an intake almost exclusively of carbohydrate as rice and fruit Such a diet is made up of carbohydrate 450 grams, protein 20 25 grams, and fat 3 5 grams per day Negative nitrogen balance occurs at first, but gradually adjustments in the metabolism occur so that a barely positive nitrogen balance is maintained Experience with such programs in diabetic patients has been limited to moderate periods, because the discomfort felt by patients has within a few weeks required an increase in the protein prescription However, despite the very high

by 'free diets," merely the omission of weighed diets but intend for the patient (notably children) to receive food suited to their metabolic needs

Protein

Normal protein ingestion lies between 60 150 grams per day Most people do not eat excessively of protein, and diabetic patients are readily satisfied by 60 125 grams of protein per day Some authorities encourage somewhat higher intakes for diabetics than the customary normal allowance of 1 gram per kilogram of body weight Some patients thus secure an improved sense of well being However, to prevent overfeeding, fat components must be markedly reduced

A common practice has been to prescribe protein approximately as follows

(1) 1 gram per kilogram ideal body weight for adult diabetics with no complications A 60 gram total daily represents the minimum, and 1 5 grams protein per kilogram body weight may be allowed for young and active adult males (2) 1 5-2 0 grams per kilogram for pregnant diabetics and for patients with exudative foot lesions, infections, protein loss or liver disease (3) Juvenile diabetics, in the period of growth, receive 2-4 grams per kilogram body weight However, these figures serve as a guide A simplified method will be outlined below (4) In the presence of nitrogen retention protein intake is kept at 40-50 grams per day as long as nitrogen retention persists, or until the nonprotein nitrogen of the blood (or urea nitrogen) has been normal for a minimum of two weeks It may then be increased, but only with frequent determinations of blood nitrogen levels

Dietary protein has been considered to yield as much as 58 per cent glucose, though at a slowed rate When one considers the concept of a common metabolic pool to which breakdown products of the three major foodstuffs contrib-

state (a) Control of weight Lowered fat intake is mandatory The diabetic just as in the normal, feeds upon his own tissues only if fat in the diet is sufficiently decreased It is to be remembered, however, that uncontrolled diabetes may be associated with excessive catabolism of both fat and protein Loss of weight should never be sought by permitting or encouraging an uncontrolled diabetic state (b) Reduction of hyperlipemia and hypercholesterolemia

There are two phases of this problem (1) In severely uncontrolled diabetes increases in total lipids and especially cholesterol in the blood plasma are frequent and occasionally excessive A striking example has been case 39428 age 18 years, who entered the Deaconess Hospital in early acidosis exhibiting lipemia retinalis, extensive xanthoma diabeticorum and a grossly creamy serum, without insulin and with persistent hyperglycemia The retinal changes disappeared dramatically in four days and the lipemia in 14 days after treatment with diet and insulin Other cases have occurred in which lipemia retinalis and a creamy fat laden serum have been associated with necrobiosis lipoidica Though marked fat restriction may be associated with slight improvement, insulin (even in the presence of a normal fat intake) completely reverses this disturbance in fat metabolism The specific effect of insulin upon the grossly disturbed fat metabolism of diabetic coma is dramatic (2) The general diabetic population contains certain numbers who have demonstrable abnormalities of cholesterol and lipid metabolism Many students of diabetes have advocated the administration of only 20-50 grams fat daily Control of total dietary intake without gross reduction in fat, plus *adequate* insulin treatment may correct partly or wholly the lipid abnormalities in some of these diabetics

(c) Prevention of degenerative vascular disease The majority of non-diabetic individuals die of some vascular lesion The development of vascular disease in the diabetic insufficiently controlled by insulin and dietary treat-

carbohydrate intake certain cases, among our younger diabetics, required reduction in their insulin dosage to avoid hypoglycemia which was directly attributable to the restriction in total calories

Fat

For most diabetics fat is regulated to supply the calories required to make up the difference between the total available from carbohydrate and protein sources and the total caloric prescription It usually varies from 50 125 grams and supplies about one third of the total calories Reduction of fat below 40 grams is not feasible because such a diet is unpalatable and difficult to obtain

Fat intake is the greatest potential source of error in estimating total calories eaten Both patient and doctor may fail here This results from the high caloric yield (9 calories per gram), from the relatively pure form in which fat containing foods occur, and from the satisfaction given Fat is so easily taken that total calories may be increased by 10 15 per cent if it is not measured or estimated with care

Although dietary fat can be greatly reduced without danger, it serves as a supply of essential fatty acids (particularly those slowly synthesized and unsaturated) and aids in the absorption of vitamins A, D, E, and K

There is seldom an indication, either in normal or diabetic persons, for increasing fat in the diet above 125 grams per day in adults The only justifiable reason would be the need for combating severe undernutrition as in tuberculosis or following long periods of inadequate control Even then, as weight approaches standard the intake should be decreased Since fat is the chief source of ketones, the diabetic may be endangered by keto acidosis, unless overfeeding is avoided

Recently, much more emphasis has been placed upon varying degrees of fat restriction The reasons given are in part well substantiated and partly still in a controversial

and (2) the binding of cholesterol by the plasma proteins themselves

For the present, factors in the body governing the metabolism of cholesterol, rather than its dietary intake, seem more closely related to the development of atherosclerosis

Lipoproteins

The significance of these large fat containing molecules in the production of vascular disease has been emphasized in a series of studies by Gofman Important facts are that diabetics frequently show abnormal lipoprotein patterns, that restricted fat intake may wholly or in part restore dis turbed patterns toward normal in non diabetics, and that in many diabetics treatment with diet and insulin usually favorably influences the levels of lipoproteins

In the diabetic, questions yet to be answered are (1) whether control of the diabetes and weight with diet and insulin will suffice to maintain normal lipoprotein patterns, and (2) will such normalized patterns, continued over the years, protect the diabetic from premature vascular disease or serve as an index of other, as yet unknown, chemical changes having a favorable effect? The most encouraging results have come from our own patients Among the 451 young diabetics studied at the Deaconess Hospital by Keiding, Root, Mann and Marble, low or normal levels of lipoproteins in the blood were found even after diabetes of 20 years duration in those patients whose diabetic control had been most faithfully maintained by diet and continued use of insulin (d) Treatment of Liver Disease Few authorities would deny the advantage of fat restriction in either normals or diabetics with parenchymal liver disease Opinions concerning the degree of fat deprivation vary considerably Allowances of 40 100 grams per day seem reasonable provided carbohydrate is not restricted below 150 grams and protein is increased by 25-50 per cent above the amount given for a similar patient without evidence of

ment may be rapid and premature Thus, advanced arteriolar sclerosis, hypertension, calcified arteries and diabetic nephropathy may be found after 10 or more years of diabetes in patients as young as 25 to 30 years Coronary arteriosclerosis is excessively frequent among diabetics *after 35 years of* age The association of alterations in the fat metabolism indicated by elevated blood cholesterol and lipoprotein values and these premature vascular lesions is becoming more evident In our young diabetics, high lipoprotein values are correlated with the degree of diabetic control Thus, the results clearly indicate that the incidence of retinitis, calcified vessels, and nephropathy was much less in the cases under good control than in those under poor control

Cholesterol

Great restriction of this normally occurring constituent of body tissues is not under normal circumstances necessary for several reasons (1) The diet must be almost fat free, cholesterol free to produce significant lowering of cholesterol levels in the blood, (2) cholesterol is still synthesized in the body by all tissues except adipose tissue and brain, but chiefly by the liver, and (3) the failure to demonstrate that the usual cholesterol intake leads in normals or diabetics to significant elevations of blood cholesterol, unless diabetes is poorly controlled

Certain diseases, i e myxedema, diabetes, nephrosis, biliary cirrhosis, familial hypercholesteremia, xanthomatoses, are often associated with marked elevations of blood cholesterol and with a *high incidence of cholesterol* containing atherosclerotic lesions Cholesterol intake may play some part in their pathogenesis, and moderate or rigid restriction of cholesterol and of total dietary fat is a reasonable adjunct in treatment

Blood cholesterol is regulated chiefly by (1) the balance of synthesis and breakdown carried on largely in the liver,

liver disease Protein intake would thus reach 100 grams per day except in rare instances Formerly, hepatomegaly occurred frequently in younger patients whose diabetes was not well controlled The use of long acting insulins has been effective in preventing it

Vitamins

The use of insulin has made adequate amounts of vitamin rich foods available to the diabetic Provided a diet balanced with fruit, vegetables, meat and dairy products is eaten, the well controlled diabetic should seldom require supplementary vitamins However, the tendency has been to consider the diabetic as needing a somewhat higher intake than the non diabetic under similar conditions No doubt, excessive administration of vitamins has occurred but such a course seems the safest until specific data is available proving the diabetic needs less Certain factors can be cited to justify current usage of supplementary vitamins

(1) Frequency of neuritis, a complication often occurring in association with or following uncontrolled diabetes Many features simulate the findings of the peripheral neuritis found in deficiency of vitamin B components, especially thiamine, niacin, and riboflavin which are essential parts in the enzymatic systems essential in carbohydrate metabolism Other portions of the B complex may also be needed, although no proof exists Deficiency of thiamine causes a decrease in an essential co carboxylase with a rise of blood pyruvic acid Since increased carbohydrate intake, in the presence of adequate insulin, also elevates blood pyruvate, a borderline supply of thiamine may become inadequate

Thiamine has been widely used for diabetic neuritis without dramatic effect Although recovery does usually occur when prolonged diabetic control is also emphasized the part played by thiamine is not clearly established

(2) The high frequency of achlorhydria and hypochlorhydria in diabetics of long duration has raised the question whether or not absorption of thiamine may be diminished At times, appetite for vitamin rich foods is lessened and supplementary vitamins may be used

(3) Decreased fat absorption Rarely does one see evidence in diabetics for any defect in ability to absorb fat, although it is well known that in patients with diabetes of long duration decrease in the external pancreatic secretions is frequent Conceivably, interference with absorption of the fat soluble vitamins A D, E, and K might follow This would apply chiefly to vitamins A and D, since E and K requirements are so readily met by an adequate diet Where fat intake is markedly curtailed in weight reduction diets, fat soluble vitamins may be administered

Occasionally in diabetic patients, especially children are seen yellow discolorations of palms, soles and nasolobial folds This is a harmless, reversible condition associated with increased blood levels of carotene The condition is called xanthosis or xanthochromia, and the mechanism of its production is unknown Treatment consists of diabetic control, restriction of carotene rich foods (egg yolk, butter, green and yellow vegetables), and restoration of the vitamins thus lost by means of a supplement

(4) Increased needs during pregnancy, lactation, infections These conditions may increase vitamin needs for the diabetic as well as for the non diabetic The former, however, can have vitamin requirements of even higher degree. Infections, in particular make the standard intake inadequate because of frequently associated uncontrolled diabetes with its poor utilization of ingested food

Certain diseases, such as hyperthyroidism, increase over all vitamin requirements

Exercise enhances vitamin C needs, but adequate dietary fruit makes supplementary vitamin C unnecessary

(5) Pellagra like lesions following antibiotics Not in frequently the use of the new antibiotic agents has produced a stomatitis and a painful swollen smooth red tongue This has suggested pellagrinous lesions such as are seen with niacin deficiency Presumably the antibiotics destroy large numbers of bacteria that may be required for intestinal synthesis of niacin Despite this attractive hypothesis the use of large quantities of B complex vitamins particularly niacin has not given the dramatic benefit expected

(6) High vitamin D requirements The diabetic will need at least as much vitamin D as the non diabetic Adults rarely require supplementary vitamin D since their daily minimal need will be satisfied by a well balanced dietary intake Children however needing a minimum of 400 international units daily should receive additional vitamin D until growth is complete (age 14 in girls age 19 in boys) Although some will eat enough liver eggs milk enriched with vitamin D and other foods containing smaller amounts of this essential vitamin there are only two safe ways to guarantee that the greater requirements are met (a) Exposure to ultra violet rays of the sun A child who is tanned has adequate vitamin D conversion of 7 dehydro cholesterol of the skin into the activated forms (activated 7 dehydro-cholesterol and activated ergosterol (b) Supplementary vitamin D This is best supplied by cod liver oil or more palatable preparations such as oleum percomorphum All growing children when not tanned or only sporadically exposed to outdoor sunlight should receive one of these preparations each day

The pregnant or lactating diabetic often requires additional vitamin D as would be supplied to the non diabetic Here the need may be met by the vitamin D contained in some multivitamin preparations which are used to fulfill other increased vitamin requirements

Clear-out examples of vitamin deficiency are rarely seen in diabetic patients today The use of vitamins need not be encouraged except in the instances mentioned above

Minerals

Adequate intake of water and the essential minerals sodium, chloride, potassium, phosphorus, calcium, magnesium, iron, sulfur, and iodine is assured in most diabetic patients by a well balanced diet, as long as the diabetes is uncomplicated

The severe depletion of water, sodium chloride and potassium during diabetic acidosis is well known For discussion of means to replenish these deficiencies see page 129

The pregnant or lactating diabetic, as well as the growing child, requires increased amounts of calcium and phosphorus Adequate milk intake in the presence of sufficient vitamin D, easily satisfies these needs with an otherwise balanced diet One pint of milk daily supplies 0 5 0 6 gram calcium and insures the required 1 0 gram daily for the average adult An additional pint will supply enough calcium for children and pregnant women During lactation still another 0 5 gram of calcium is best supplied by further addition of milk or its products If appetite will not allow such intakes of calcium, supplementary oral calcium may be given

Because of the high incidence of achlorhydria in diabetics, iron absorption may be significantly diminished Iron and acid should both be administered in such cases' Normally, however, adequate food intake supplies adequate iron In the presence of hypochromic anemia or with the increased needs of pregnancy and lactation, supplementary iron is required

Management of the Diet

One may assume the new diabetic knows nothing of what or how much he should eat Make him diet conscious at the outset by carefully recording his food intake, types of food, their amounts, and the time of day when eaten Do not expect to calculate accurately what has been eaten, but

a rough estimate of carbohydrate intake and of any gross dietary aberrations—especially protein, vitamins, minerals—is promptly available Also, one gains insight into the patient's intellect and background, as well as learning more about his most cherished eating habits or of some other illness such as duodenal ulcer for which the diet has been changed Discover the reasons for deviations from an average, adequate diet, particularly those engendered by economic or social limitations or by an unusual daily schedule

Remember how simple the diabetic diet may be, and prove it to the patient by giving only the most important instructions at first and in a clear fashion These major points should be written down, just as a complete dietary outline is best given in writing Teach that over feeding is being eliminated, thus giving assurance of an adequate rather than a starvation diet

Emphasize what is to be eaten and how much, not what to avoid This positive approach plus an understanding by the patient of the aims in a controlled diet is the best guarantee that the program will be followed Obviously, a diet not followed is no diet at all

The outline to follow describes (1) Calculation of the diet as to total calories—carbohydrate, protein and fat based on age, sex weight and activity for the uncomplicated diabetic, and (2) making up the diet to specify the exact foods and their amounts to fit the calculated requirements Do not expect the calculations to be correct with the first, or even the second try Rather anticipate the need for periodic changes and be ready to make these promptly Thus, ultimately the diet fits the individual patient, for seldom, if ever, will one find two persons whose daily intake can be made identical for more than a day

Calculation of the Diet, Table 2 Ideal weights for age, height and sex

There are many ways of making these calculations However, they are all based upon an estimate of *basal* caloric requirements with adjustments up or down depending upon age, sex, the presence of under- or overweight, and *activity* Some of these methods include

(1) Determination of basal 24 hour caloric requirements To this caloric figure is then added a certain percentage based on the estimated daily activity Higher or lower corrections are then made on the basis of deviation in body weight below or above the ideal

(2) Approximation of basal 24 hour caloric requirements This is done by multiplying the ideal weight in pounds by 10 (see Table 2) This figure is then adjusted by adding or subtracting an arbitrary number of calories based on age, sex, and body build It is further changed according to the *estimated* activity

(3) Overall estimate of 24 hour caloric requirement per kilogram ideal body weight Again, these estimates vary greatly from one authority to another

It is evident that a single *correct* method does not exist, short of the almost impossible task of actually determining the elimination of total calories during a patient's average day, because of the human error involved in (a) attempting to *estimate* activity and in (b) planning an arbitrary *rate* of gain or loss in weight

Since absolute accuracy is impossible, experience here has shown two factors to be paramount 1 *Simplicity* 2 A basic diet to be added to or subtracted from, as a *starting point* For simplicity, allow 25 calories per kilogram ideal body weight (growing children excepted) With very little experience, calculation can be done without paper in a matter of seconds For the outline of the basic diet see page 54

An easy series of steps to arrive at the diet figures

TABLE 2

Maximum Longevity Tables

Ideal Weights for Men Aged 25 and Over

Height (with shoes)		Weight in pounds (as ordinarily dressed)		
Feet	Inches	Small Frame	Medium Frame	Large Frame
5	2	116-125	124-133	131 142
5	3	119 128	127 136	133-144
5	4	122 132	130-140	137 149
5	5	126-136	134-144	141 153
5	6	129 139	137 147	145-157
5	7	133-143	141 151	149 162
5	8	136-147	145-156	153-166
5	9	140-151	149-160	157 170
5	10	144-155	153-164	161 175
5	11	148-159	157 168	165-180
6	0	152-164	161 173	169 185
6	1	157 169	166-178	174 190
6	2	163-175	171 184	179-196
6	3	168-180	176-189	184-202

Ideal Weights for Women Aged 25 and Over

Height (with shoes)		Weight in pounds (as ordinarily dressed)		
Feet	Inches	Small Frame	Medium Frame	Large Frame
4	11	104-111	110-118	117 127
5	0	105-113	112-120	119 129
5	1	107 115	114-122	121 131
5	2	110 118	117 125	124-135
5	3	113-121	120 128	127 138
5	4	116-125	124-132	131 142
5	5	119-128	127 135	133-145
5	6	123 132	130-140	138-150
5	7	126-136	134 144	142-154
5	8	129 139	137 147	145-158
5	9	133-143	141 151	149-162
5	10	136-147	145-155	152-166
5	11	139 150	148-158	155-169
6	0	141 153	151 163	160-174

(Metropolitan Life Insurance Co.)

(adults) would be (a) Find the ideal body weight for the patient s age, sex, height, and body build (see Table 2) With experience, an accurate estimate can be made when such a table is not at hand Two factors are helpful in making such an estimate (1) a statement from the patient as to his or her weight when at the peak of physical condition, and (2) estimate the amount by which current weight is above or below the ideal and then subtract from or add to the current figure At the start, such estimates are particularly justified because so often the diabetic is grossly overweight Also, he is reassured that his own ideas concerning his ideal weight are being given due consideration (b) Calculate total calories, i e Ideal weight in kg × 25 (cal /kg allowed = total calories (c) For carbohydrate, take 10 per cent of the total caloric figure Thus, if total calories to be allowed are 1500, then 10 per cent of 1500 = 150 grams carbohydrate However, empirically keep the range of carbohydrate between 150 and 200 grams in most instances (d) Allow protein as previously indicated 1 gram /kg ideal body weight will be the usual amount (e) Make up the remaining caloric requirement with fat *Thus*, calories to be obtained from fat = total calories minus total of calories from carbohydrate plus calories from protein

Then Calories to be obtained from fat divided by 9 = grams of fat

Example A 50 year old woman, weight 176 pounds (80 kg), ideal weight 132 pounds (60 kg)

(a & b) Total calories = Ideal weight 60 kg × 25 (cal / kg) = 1500 calories
(c) Carbohydrate = 10 per cent × total cals 1500 = 150 grams
(d) Protein = Ideal weight 60 kg × 1 (gm /kg) = 60 grams
(e) Fat

Total Calories =		1500
Calories from protein = 60 grams × 4	= 240	
Calories from carbohydrate = 150 grams × 4	= 600	
Calories from protein and carbohydrate	= 840	840
		660
Calories to be derived from fat	=	660

$$\frac{\text{Calories from fat } 660}{9 \text{ (cal /gm)}} = 73\ 3$$

Her diet would thus be C 150 P 60 F 73 = 1497 calories

The diet prescribed could well be the *Basic Diet*, outlined below

Remarks A Because all foods will vary somewhat in their carbohydrate, protein and fat contents—and since the calculated diet is an *estimate*

(1) Fractions of grams are meaningless amounts and should be dropped

(2) Even though the basic diet contains C 153 P 69 F 76 = 1572 calories, there is no need for bizarre changes in the food prescribed in order to make the figures identical with the calculated prescription above

B Note that no mention was made of this woman's activity This is because she was so grossly overweight that at least half of her weight reduction should easily be accomplished with this diet If it later turned out that her weight would fall only a fraction of the amount desired and that she was sedentary in her daily life, then her diet could be further reduced by allowing only 15 20 cals /kg Such a change would require further reduction in fat intake and even a cautious lowering of carbohydrate *For example* At 20 cals /kg ideal wgt Total cals = 20 × 60 = 1200 Using the basic diet simply omit cream (12 Gm) and butter (25 Gm), thus leaving out 37 Gm of fat or 333 calories

By simple subtraction her diet would then be

	Basic Diet		Cream & Butter		Final Diet at 20 cals /kg
Carb	153	minus	2	=	151
Prot	69	minus	2	=	67
Fat	76	minus	37	=	39
Calories	1572	minus	349	=	1223

C It can be seen that this modification will not significantly alter the patient's nutrition in terms of the critical needs for protein, vitamins and minerals

Usually it is well to start with total calories and carbohydrate 10-15 per cent below the calculated ideal This serves to hasten reduction in hyperglycemia and glycosuria, allowing the doctor to tell the patient that before long some increases in diet may be made—a further boost to patient morale

Children (up to age 14 in girls, age 19 in boys)

Again there are many ways to calculate the needs of a child Most of these are based on (1) a given number of calories per kilo ideal body weight—infants 100, 75 at age 5, 50 at age 10, 40 at age 15 until adulthood, (2) height—35 calories per inch, and (3) age This method is outlined below as it seems the simplest

Calculation

(1) 1000 cals allowed for age 1 year

(2) Additional 100 cals allowed for each yr of age above age 1

(3) 10% of the total caloric figure given as gms carbohydrate, with a maximum of 225-230 gms

(4) Protein and fat = about ½ the figure for carb At age 13 these are further increased to make up total caloric prescription for boys

Example Child age 5 years

1000 + (100 × 4 (yrs of age above 1) = 1000 + 400 = 1400

(3) 10% of 1400 cals = 140 gms (the carb figure)

(4) ½ × 140 = 70 gms each of protein and fat

Sample Diet C 140 P 60 F 70 (approximately)

10 gm carbohydrate at mid-morning, mid afternoon, and bedtime

Changes in between meal feedings are determined by 1) Type of insulin, 2) Timing of meals, 3) Nocturnal glycosuria

Carbohydrate usually is distributed ⅓-⅓-⅓, but may be ⅕ ⅖ ⅖ Between-meal feedings are subtracted from principal meals Thus, final carbohydrate distribution for a C 150 diet would be either *40 10-40-10-40 10* = *150* grams or *20*-10 50-10-50-10 = 150 grams

Food Prescriptions

The basic diet as previously mentioned is outlined below Remember that such a program has been chosen chiefly because it conforms generally to the eating habits of many people in this country, will allow an even distribution of *carbohydrate and caloric intake, and is well-balanced to* satisfy most vitamin and mineral needs Supplementary instructions must be supplied if the patient is to use his diet prescription properly

A *Measurement*

Food must be correctly measured Preferably this means all food to be eaten (excepting uncooked 3% vegetables and 6% vegetables) However, many persons have an occupation or other factors in their personal life making this impossible, but even they should be urged to measure one or several meals as the opportunity arises Only in this way can wide oscillations from day to day be avoided

TABLE 3

A BASIC DIET IN PORTIONS, GRAMS, CARB. C PROTEIN P. FAT F

Food	Portion	Weight Gms	Grams in Each Portion C	P	F	Total Daily Portions	Total Grams C	P	F	Total Calories
Orange	1 medium	150	15	0	0	2½	40	0	0	160
Bread	1 slice	30	15	2 5	0	3	45	7 5	0	210
Oatmeal	1 medium	15	10	2 5	1	1	10	2 5	1	69
Milk	10 oz	300	15	10	10	1	15	10	10	190
Cream light	1 oz	30	1	1	6	3	3	3	18	186
Egg	1	60	0	6	6	1	0	6	6	78
Meat	1 small	60	0	14	10	2	0	28	20	292
Butter	1 teaspoon	5	0	0	4	5	0	0	21	189
Vegetables 3% and 6%	1 cup	150	5	2 5	0	4	20	10	0	120
Uneeda Crackers	2	30	10	1	0	2	20	2	0	88
						Approximately =	153	69	76	1572

TABLE 4

To distribute the above allowances the following outline is highly workable
* See below for Between Meal

Breakfast Food	Portions	Grams	Dinner Food	Portions	Grams	Supper Food	Portions	Grams
Eggs	1	60						
Meat, cooked		or		2 oz small	60		2 oz small	60
Bacon	2 strips	14						
Oatmeal dry		15 or						
Oatmeal cooked	½ cup	120						
Milk	2 oz	60						
Cream	2 tbsp	30		2 tbsp	30		2 tbsp	30
Butter	1 tsp	5		2 tsp	10		2 tsp	10
Orange	1 small	100		1 medium	150		1 medium	150
Bread	1 slice	30		1 slice	30		1 slice	30
Uneedas								
3% Vegetables				large cup	200		large cup	200
6% Vegetables				½ cup	100		½ cup	100

*Between Meal

(4 P M 10 P M)	4 P M		10 P M	
Food	Portions	Grams	Portions	Grams
Milk	½ cup	120	½ cup	120
Uneedas	2	30	2	30

Weighing

Every diabetic—fat or thin rich or poor young or old—*should be urged to weigh his daily diet* Better that he buy a scale to weigh his food than weigh himself Many can and will weigh all food all the time For those who cannot show them the value of weighing at the start for days or weeks and then periodically—at intervals of 1 2 months—returning to the scale as a check upon their estimates during the interim

Type of Scale—Where Obtained The gram scales manu factured by John Chatillon Co New York have been found satisfactory

Household Utensils

With the standard 8 oz measuring cup teaspoon and tablespoon most foods can be measured with reasonable accuracy *No doubt most patients who trouble to do any* measuring use this system However certain foods still defy accuracy without a scale viz meat fruit ADA substitution *plan will be discussed below*

B *Timing of Meals*

The importance of eating meals distributed at even inter vals throughout the waking day and at the same time every day cannot be overemphasized especially for those taking insulin Omission of or delay in eating all too frequently may lead to a severe hypoglycemic reaction Patients who consistently do this and boast of having no trouble are ad mitting poor diabetic control

Do not allow the patient on diet alone to be more lax Feeling secure in the knowledge that insulin reaction does not concern him he will often curtail eating at one time of *day in order to save up for a big meal or extra snacks* En couraging him to test his urine an hour after his 'big meal" will usually demonstrate the error of his ways

Theoretically, a total 24 hour allowance would best be taken in equal parts every one to two hours, but such a plan is impractical Experienced patients may be allowed to increase between meal feedings by omitting equivalent amount from preceding meal

C *Between Meal Feedings*

Such feedings are necessary to satisfy the habits of most people and to help avoid hypoglycemia for those taking insulin The extra food is usually subtracted from the preceding meal *unless* it has been given to *correct* hypoglycemia If the carbohydrate given for a reaction is only 5-10 gms greater than the usual between meal feeding and the urine test is sugar free or nearly so before the next meal, then be sure that meal is all eaten If, however, the extra carbohydrate is excessive as indicated by the urine test before the next meal (i e, yellow, orange, brown, red), then subtract 50 100% of the *extra* carb amount from the succeeding meal

The routine use of between meal feedings must be individualized but in general will best be distributed as shown in Table 5

Note that some of the suggested feedings contain some protein and fat as well as carbohydrate This is desirable because of the slowed rate at which these food elements make carbohydrate available Obviously the examples given are only a few of the many possibilities to give variety

Because of their great activity most growing children require 10-15 gms of carbohydrate between meals and at bedtime

For those using PZI, Globin, or NPH *alone* the carbohydrate needed for between meal feeding may be taken from the breakfast, especially when glycosuria habitually occurs before the noon meal

Sometimes the administration of the same long active insulin twice in 24 hrs may be required There are some

TABLE 5

Patients Taking Insulin Before Breakfast	Time of Feeding	Amt Carb	Example
PZI	Bedtime	10-15 Gms	2 Uneedas and 120 Gms Milk
PZI & C I (Separately)	Bedtime Occas Mid A M	10-15 Gms	or 2 Uneedas and 100 Gms Orange
NPH	Mid P M and usually bedtime	10-15 Gms	or 4 Saltines and 90 Gms Pear (small)
Globin	Mid P M	10-15 Gms	or 4 Saltines and 120 Gms Milk
PZI & C I (Mixed)	Mid P M and usually bedtime	10-15 Gms	or 90 Gms Pear and 120 Gms Milk
NPH & C I (Separate or Mixed)	Mid P M and usually bedtime	10-15 Gms	or 50 Gms Banana (½) and 120 Gms Milk
Labile or Brittle diabetes	Hourly when awake	3-10 Gms	as Uneedas Saltines Soda Crackers etc

unstable patients who seem to do best with NPH before breakfast a[illegible] at supper [illegible] all such cases distribution [illegible] l feed[illegible] be based on individual [illegible]

[illegible] Ca[illegible]

[illegible]le [illegible] foods on

[illegible] aid in

[illegible] con-

TABLE 6

Approximate Substitutes for Foods on Diet Sheet

Substitutes for 1 ounce (30 grams) of *lean* meat (any kind)

- 1 egg
- 2 medium sized strips bacon (15 grams)
- 1 ounce fish or fowl (30 grams)
- 5 oysters clams shrimps scallops (all small) plus 1 teasp butter
- 1 ounce or 1 slice American cheese (30 grams) omit 1 teasp butter
- 1 ounce creamed cottage cheese (30 grams)
- 1 tablespoon peanut butter (15 grams)
- 2 ounces meat = 1 pound live chicken lobster plus 2 teaspoons butter

Substitutes for two Uneedas (food value of following = 10 gms carbohydrate)

- 2 plain graham crackers
- 2 double squares Ry Krisp (13 gms)
- 3 Arrow Root biscuits
- 4 saltines
- 5 Ritz
- 3 Ginger snaps
- 15 oyster crackers
- ½ slice bread (20 gms)
- ½ cup cooked oatmeal
- 12 gms dried prepared cereal (cornflakes etc)
- 100 gms orange

Substitutes for 1 slice bread (30 gms) (food value of following = 15 gms carb)

- 2½ ounces potato (75 gms)
- Add 20 grams to baked potato to allow for skin
- ½ cup corn lima beans shell beans (75 gms)
- ¾ cup parsnips
- ½ cup cooked rice (75 gms)
- ½ cup cooked macaroni spaghetti noodles
- 1 medium bran muffin
- 30 gms pumpernickel (1 slice)
- 1 Pilot cracker
- 1 Matzoth (20 gms)
- 150 grams orange
- 1 small corn muffin (30 gms)

Substitutes for 1 teaspoon butter (5 grams) (Food value of following = 4 gms fat)

- 1 teaspoon margarine
- 1 teaspoon mayonnaise
- 1 teaspoon salad oil
- 1 teaspoon peanut butter
- 1 tablespoon light cream (15 gms)
- 2 teaspoons cream cheese
- 1 slice bacon

For 2 teaspoons butter 1 tablespoon sour cream or 1 tablespoon heavy cream

FRUIT SUBSTITUTIONS

In Place of 100 Grams of Orange (Small)	In Place of 150 Grams of Orange (Medium)
½ medium grapefruit (150 gms)	1 medium grapefruit (225 gms.)
1 cup strawberries (150 gms)	1½ cups strawberries (225 gms)
¾ cup watermelon (150 gms)	1 cup of watermelon (225 gms)
⅓ cantaloupe (150 gms)	½ cantaloupe (225 gms)
½ cup blackberries (120 gms)	¾ cup blackberries (180 gms)
1 small pear (90 gms.)	½ medium papaya (150 gm)
½ cup raspberries (8 gms)	¾ cup raspberries (120 gms)

TABLE 6—Continued

½ cup blueberries ([illegible] gms.)
1 medium peach ([illegible] gms.)
¼ cup stewed apricots ([illegible] gms.)
2 medium plums ([illegible] gms.)
¼ cup pineapple ([illegible] gms.)
¼ cup applesauce ([illegible] gms.)
¼ honeydew melon ([illegible] gms.)
½ small Mango (35 gms.)
9 cherries ([illegible] gms.)
½ small banana (50 gms.)
3 prunes without sugar (50 gms.)
Jello (50 gms.)
Ice Cream (vanilla) (50 gms.)

¾ cup blueberries (105 gms.)
1 medium pear (135 gms.)
1½ medium peach (135 gms.)
½ cup stewed or 2 ripe apricots (120 gms.)
3 medium plums (120 gms.)
½ cup or 2 slices pineapple (105 gms.)
1 small apple (105 gms.)
½ cup applesauce (without sugar)
¼ honeydew melon (105 gms.)
¾ small Mango (90 gms.)
13 cherries (90 gms.)
¾ banana (75 gms.)
5 stewed prunes without sugar (75 gms.)
75 grams Jello
small serving of Ice Cream (75 gms.)
(Use not more than once a week.)

All fruits fresh or water packed. All fruit juices unsweetened. All fruits cooked without sugar.

ADDITIONAL APPROXIMATE SUBSTITUTIONS FOR FOODS ON DIET SHEET

Most Foods Are a Combination of Carbohydrate, Protein and/or Fat

Carbohydrates		*Proteins*	*Fats*
Sugar	Starch	Lean Meats	Butter
Fruits	Vegetables	Fish—Fowl	Cream
Bread	Rice	Egg	Cream Cheese
Cereal	Milk	Cheese	Bacon
Macaroni	Flour	Cottage Cheese	Oil
			Lard

Household

30 grams = 1 ounce
5 grams = 1 teaspoon
3 1 tblsp.
2 tb gms = 1 oz

240 grams =
180 grams =
grams =
grams =

Diabetic and on F
Manual.

1. C *egetable*
plu. water)
75 one
1 U

2. *Cream*
150
3. *Clam C*
1

TABLE 6—Continued

4 *Baked Custard* 120 gms (made with Sucaryl) = 100 gms orange plus 1 oz meat or 6 oz milk
5 *Sponge Cake (Plain)* 30 grams = 1 slice bread—use occasionally or 150 gms orange
6 *Beans and pork (canned)* ½ cup (130 grams) = 1 slice bread plus 2 vegetables at one meal plus 2 teaspoons butter

3 P M Lunch—2 Uneedas plus 4 oz milk =
a 12 gm prepared cereal plus 4 oz milk

ITALIAN SPAGHETTI

½ cup cooked spaghetti = 1 slice bread or 2½ oz potato
2 oz meat (Hamburg) = 2 oz meat portion Extra meat used as cheese
Omit butter from meal

Sauce ½ cup tomatoes plus ½ cup tomato paste = 1 cup 3 per cent vegetable and ½ cup 6 per cent vegetable at meal
Season as desired

tained in bread, cereal, fruit, milk, vegetables, etc , *Protein* found in meat, cheese, eggs, nuts, etc *Fat* occurs largely in butter, mayonnaise, margarine, grease, cream, and olive oil Overlapping of these food components is more frequent than not, so that the patient must know he is also eating fat when meat or cheese is consumed and that whole milk has more carbohydrate than either protein or fat, etc

Remind the patient that a slice of bread contains as much carbohydrate as three lumps of sugar and that an ounce of meat contains more calories than a slice of bread. Many similar comparisons will soon drive home the fallacy of following a purely qualitative diet

(2) Additions to diet without food value—these include coffee, tea, pickles (unsweetened dill, or sour), clear broths, bouillon (no fat), gelatin, rennet tablets, uncooked 3% vegetables, salt & pepper, ketchup, vinegar, mustard, cinnamon, nutmeg, garlic, mint, parsley, lemon, and others Saccharin, Sucaryl, or Saxin may be used to sweeten "

Special diabetic foods—excepting water packed canned

fruit which is mandatory—are better avoided than encouraged Though most of these are now labeled to give contents of carbohydrate, protein, and fat, they are expensive and too often replace the more nourishing natural foods allowed in the diet However, it is helpful to give children a conservative allotment of the especially prepared hard candy, chewing gum or soft drinks

(3) The diabetic diet need not be a bizarre assortment of food to fit exactly the allowed amounts of the food components Simply let the patient eat the same foods as are desirable and adequate for the others in his household These foods are then measured in accordance with his diet prescription, omitting only the well known excessive sources of carbohydrate still allowable for others in the family

E Supply written tables giving equivalent values of foods to be substituted for those in the basic diet These should give three sets of figures (Table 7) The first lists vegetables in 3%, 6% and 20% groups and the amounts of fruit to be substituted for the "orange" used as an example in the basic diet

The 3% vegetables may be taken in unlimited quantities except when cooked, when a large cupful is adequate However, intake of 3% vegetables may be doubled if one omits the 6% vegetable

Fruit may be taken in any form—cooked, canned, fresh, frozen or dried—as long as it has had "no sugar added" The weight of fruits listed refers to the edible portion Vegetable weights are taken after cooking except for those eaten raw —celery, lettuce, etc

The third table gives a list of ... only desired approximate substitut... r foods on ... diet

The th ... for the ... enced and intelligent pati ... rapidly ... ubstitutions from such a list ... small ... rd The doctor ... uld kno ... or ... available for ... ce I ... tab ... n a small

TABLE 7

FOOD VALUES

Vegetables and Fruits According to Content of Carbohydrate

VEGETABLES fresh or canned	
3 per cent	
Lettuce	Tomatoes
Cucumbers, raw	Radishes
Spinach	Water Cress
Asparagus	Snap Beans
Celery	Cauliflower
Mushrooms	Cabbage
Rhubarb	Egg Plant
Sauerkraut	Broccoli
Endive raw	Green Peppers
Swiss Chard	Kohl Rabi
Beet Greens	Kale
Dandelions	Summer Squash
6 per cent	20 per cent
Turnip	Potatoes
Carrots	Shell Beans
Okra	Baked Beans
Pumpkin	Lima Beans
Onions	Corn
Squash	Boiled Rice
Brussels Sprouts	Boiled Macaroni
Beets	
Green peas	

FRUITS fresh or canned (water packed)		
Food	Carb 10	Grams 15
Grapefruit Pulp	150	225
Strawberries	150	225
Watermelon	150	225
Cantaloupe	150	225
Blackberries	120	180
Orange Pulp	*100*	*150*
Pears	90	135
Peaches	90	135
Apricots	80	120
Raspberries	*80*	*120*
Plums	80	120
Pineapple	70	105
Apple	70	105
Honeydew Melon	70	105
Blueberries	70	105
Cherries	60	90
Banana	50	75
Prunes (cooked)	50	75

1 gm carbohydrate 4 calories
1 gm protein 4 calories
1 gm fat 9 calories

1 kilogram (kg) = 2.2 lbs 30 grams (g) or cubic centimeters (cc) = 1 oz A patient at rest requires 25 calories per kg

Carbohydrate Protein Fat and Calories in Common Foods

30 Grams 1 oz Contain Approximately	Carb C Grams	Protein P Grams	Fat F Grams	Calories
Bread 1 large slice	15	2.5	0	70
Oatmeal large portion	20	5	2	118
Crackers	20	3	2	110
Vegetables 3% + 6% 4 large portions	20	6	0	104
Potato	6	1	0	28
Milk	1.5	1	1	19
Egg 1	0	6	6	78
Meat lean	0	7	5	73
Chicken lean	0	8	3	59
Fish fat free	0	6	0	24
Cheese	0	8	10	122
Bacon	0	5	15	155
Cream 20% (light)	1	1	6	62
Cream 40% (heavy)	1	1	12	116
Butter or margarine	0	0	25	225

mate the calculated need Such a diet might be (C 212 P 108 F 107)

B	10 A M	D	3 P M *	S	Bedtime
1 egg	2 Uneedas	90 meat	2 Uneedas	120 meat	2 Uneedas
15 bacon		200 3% veg	120 milk	200 3% veg	
15 oatmeal		100 6% veg		100 6% veg	
10 butter		10 butter		10 butter	
60 cream		180 milk		180 milk	
120 milk		150 orange		150 orange	
150 orange		75 potato		75 potato	
30 bread		30 bread		30 bread	

* This distribution would be especially suitable with NPH insulin

D The 13 year old girl is now 17 years old, has stopped growing and has been gaining weight steadily on the diet above The diet must be reduced carefully to allow a fall in weight toward her ideal, which may be 132 pounds Theoretically, the basic diet would do, but in practice it would be insufficient because of the great activity customary at this age Here it is safest to head for some point between the basic C 153 P 69 and F 76 and her former C 212 P 108 F 107 A good share of the caloric decrease is best done chiefly by lowering fat, thus removing a minimum of high *vitamin content foods One could simply* reduce butter to 5 gms (5 gms at a meal), omit the cream, reduce supper meat to 90 grams, and leave out one potato

Then

	C	P	F	less	C	P	F
	212	108	107		0	7	5
		− 12	− 29		0	0	12
					2	2	12
			78		15	3	0
Leaving			F 78		17	12	29

The been at age 22

es are 30

o of 180 250

be

almost identical with her eating at age 13, but should be reduced in calories (if weight increases 20 lb or more) by cutting down on fat (skim milk in place of whole milk often suffices)

The diets described are but a few of the abundant variations possible, but they show the profound changes brought about by specifying a little of this or that food to be added or subtracted

Make the diet fit the patient (rather than any calculated need), and above all judge its effect by the urine test for sugar

The Food Exchange System

In 1950 a joint committee of the American Diabetes Association, American Dietetic Association, and the Diabetes Section of the United States Public Health Service published * a simplified method for calculating diabetic diets and planning diabetic menus With their joint approval many hospitals and physicians have adopted this newer method in the instruction of diabetic patients The values agreed upon are listed below and the manner in which the *basic diet* above would be prescribed using this system is outlined

The foods commonly used in dietary prescriptions are divided into six groups Within each group are given the kind and amounts of food of about the same nutritional value in carbohydrate, protein and fat Thus, any item within that group may be exchanged with any other item in that group but not with foods from other lists The following figures are used in calculating diabetic diets

* Revised Table of Food Values Proc Am Diabetes Assn, 9 403, 1949

TABLE 9

FOOD VALUES FOR CALCULATING DIABETIC DIETS

Group	Amount	Weight gm	Cho gm	Protein gm	Fat gm	Energy calories
Milk, whole (List 1)	½ pint	240	12	8	10	170
Vegetable (List 2A)	as desired	—	—	–	—	—
Vegetable (List 2B)	½ cup	100	7	2	—	36
Fruit (List 3)	varies	—	10	–	—	40
Bread Exchanges (List 4)	varies	—	15	2	—	68
Meat Exchanges (List 5)	1 oz	30	—	7	5	73
Fat Exchanges (List 6)	1 tsp	5	—	–	5	45

Certain foods with special value should be included in each day's diet These include milk, at least one serving of meat, fish, fowl, eggs or cheese, whole grain cereal, fruit, vegetables—green or yellow and butter

TABLE 10

FOOD EXCHANGES

LIST I MILK

Carbohydrate 12 gm., protein 8 gm, fat 10 gm per serving

Food	Approx Measure 1 Exchange	Weight Gm
Milk	1 cup (8 oz)	240
Milk, evaporated	½ cup	120
Milk, powder, whole	¼ cup (4 tblsp level)	35
*Buttermilk	1 cup	240
*Milk, skim	1 cup	240

* Add 10 gm. fat (2 fat exchanges) to make equivalent of whole milk Most commercial buttermilk is skimmed Check local supplies

LIST II VEGETABLES

One or more fat exchanges from the diet allowance may be used to season the vegetables

A VEGET le carboh and fat in amounts ordinarily u

If more th ked fo ne meal, it should be calculated as roup B

Asparagus	Mu	*Watercress
coli	Okr	*Greens
ssels sprou	P	Beet greens
age	ep	hard

TABLE 10—Continued

Cauliflower	Radish	Collards
Celery	Romaine	Dandelion
*Chicory	Rhubarb	Kale
Cucumber	Sauerkraut	Mustard
*Escarole	String beans	Poke
Eggplant	Summer squash	Spinach
Lettuce	*Tomatoes	Turnip greens

B Vegetables—carbohydrate 7 gm, protein 2 gm, fat negligible per serving
1 exchange = ½ measuring cup = 100 gm

Beets	Peas green	*Squash, winter
*Carrots	Pumpkin	Turnip
Onions	Rutabagas	

* These vegetables have high vitamin A content, use at least one serving each day

LIST III FRUITS

Fresh, cooked, canned or frozen *unsweetened*
Carbohydrate 10 gm per exchange, protein and fat negligible

Fruit	*Approx Measure 1 Exchange*	*Weight Gm*
Apple, 1 small	2 ′ dia	80
Applesauce	½ cup	100
Apricots, fresh	2 medium	100
Apricots, dry	4 halves	20
Banana	½ small	50
Berries (Blackberries Raspberries and *Strawberries)	1 cup	150
Blueberries	⅔ cup	100
*Cantaloupe	¼ (6 dia)	200
Cherries	10 large or 15 small	75
Dates	2	15
Figs, dried	1 small	15
Figs, fresh	2 large	50
*Grapefruit	½ small	125
*Grapefruit juice	½ cup	100
Grapes	12	75
Grape juice	¼ cup	60
Honeydew melon	⅛ (7″ dia.)	150
Mango	½ small	70
Nectarines	1 medium	100
*Orange	1 small	100
*Orange juice	½ cup	100
Papaya	⅓ medium	100
Peach	1 medium	100

TABLE 10—Continued

Pear	1 small	100
Pineapple	½ cup, cubed	80
Pineapple juice	⅓ cup	80
Plums	2 medium	100
Prunes, dried	2 medium	25
Raisins	2 tblsp level	15
Rhubarb	(see LIST II A)	
*Tangerine	1 large	100
Watermelon	1 cup, diced	175

* These fruits are rich sources of vitamin C, use at least one serving each day

LIST IV BREAD EXCHANGES

Carbohydrate 15 gm, protein 2 gm, fat negligible

Food	*Approx Measure 1 Exchange*	*Weight Gm*
Bread, baker's	1 slice	30
Biscuit, roll	2′ dia	35
Muffin	2″ dia	35
Cornbread	1½″ cube	35
Cereals, cooked	½ cup, cooked	100
Cereals, dry (flakes, puffed and shredded varieties)	¾ cup, scant	20
Rice, macaroni, noodles, spaghetti	½ cup, cooked	100
Crackers		
Graham	2 (2½ x 2¾″)	20
Oyster	20 (½ cup)	20
Saltines	5 (2″ square)	20
Soda	3 (2½ x 2½)	20
Round, thin varieties	6 (1½′ dia)	20
Vegetables		
Beans, peas dried (cooked) Includes limas, navy, kidney beans, blackeyed, cowpeas and split peas, etc	½ cup, scant	100
Corn	⅓ cup or ½ ear	80
Popcorn	1 cup, heaping	20
Parsnips	½ cup	125
Potatoes		
White, baked	2″ dia.	100
White, boiled, mashed	½ cup	100
Sweet or ya[illegible]	¼	50
Desserts		
*Ice cream,	½	70

* Omit 2 fat

TABLE 10—Continued

LIST V MEAT EXCHANGES

Carbohydrate neglıgible, proteın 7 gm., fat 5 gm per servıng
Note All ıtems are expressed ın cooked weıght. One or more fat exchanges from the dıet may be used to cook or season these foods.

Food	Approx Measure 1 Exchange	Weight Gm
Meat		
Beef, fowl, lamb, veal (medıum fat), lıver, pork, ham (lean)	1 oz	30
Coldcuts		
Salamı, mınced ham, bologna, cervelat, lıver sausage, luncheon loaf	1 slıce 4½ ' dıa. x ⅛ '	45
Frankfurter (8-9 per lb)	1	50
Fish		
Cod, haddock, halıbut, herrıng etc	1 oz	30
Salmon, tuna, crabmeat, lobster	¼ cup	30
Shrımp clams, oysters (medıum)	5	45
Sardines	3 medıum	30
Cheese		
Cheddar type	1 oz	30
Cottage	3 tblsp , level	45
*Peanut butter	2 tblsp , scant	30
Egg	1	50

* Lımıt to one servıng per day unless adjustment ıs made to balance carbohydrate content

LIST VI FAT EXCHANGES

Carbohydrate and proteın neglıgıble, fat 5 gm. per servıng

Food	Approx Measure 1 Exchange	Weight Gm
Avocado	4 ' dıa , ⅛	20
Butter or margarıne	1 tsp , level	5
Bacon, crısp	1 slıce	10
Cream, lıght, sweet or sour—20%	2 tblsp	30
Cream, heavy—40%	1 tblsp	15
Cream cheese	1 tblsp , level	15
French dressıng	1 tblsp	15
Mayonnaıse	1 tsp.	5
Nuts	5 small	5
Oıl or cookıng fat	1 tsp	5
Olıves	5 small	50

A sample diet containing carbohydrate 152, protein 63 and fat 80 grams is as follows:

Total Day's Food

List 1	Milk, 1½ servings
List 2A	Vegetables, as desired
List 2B	Vegetables, 2 servings
List 3	Fruits, 3 servings
List 4	Bread exchanges, 6 servings
List 5	Meat exchanges, 5 servings
List 6	Fat exchanges, 8 servings

Divide the day's food into meals

Breakfast	*Exchange Lists—No Servings*						
	1	*2A*	*2B*	*3*	*4*	*5*	*6*
Orange juice—½ cup				1			
Toast—1 slice					1		
Butter—1 teaspoon							1
Oatmeal, cooked—½ cup					1		
Milk—½ cup	½						
Cream, light—2 tablespoons							1
Egg—1						1	
Coffee	—	—	—	—	—	—	—
Lunch Meat—2 ounces						2	
Lettuce and Tomato ad lib	—	freely	—	—	—	—	—
Peas—½ cup			1				
Bread—1 slice					1		
Butter—1 teaspoon							1
French dressing—1 teaspoon							1
Apple—1 small				1			
Cream—2 tablespoons							1
Coffee or Tea	—	—	—	—	—	—	—

Supper	*Exchange Lists—No Servings*						
	1	*2A*	*2B*	*3*	*4*	*5*	*6*
Meat—2 ounces						2	
Spinach cooked—1 cup		1					
Carrots—½ cup			1				
Bread—1 slice					1		
Butter—2 teaspoons							2
Strawberries—1 cup			—	1			
Cream—2 tablespoons							1
Coffee	—	—	—	—	—	—	—
4 P.M and Bedtime Graham crackers—2					2		
Milk—½ cup	1						
Total Servings =	1½	as desired	2	3	6	5	8

It is evident that the patient then needs but two things to follow a varied diet 1) The number of servings to use from each list for his three meals and between meal feed ings, and 2) the written lists for reference

Emergency Feedings

During acute infections or on resumption of eating after surgery, a reduced diet of about carbohydrate 150 protein 50 and fat 50 grams may be offered Emphasize milk, fruit juices or ginger ale, eggnogs, cooked cereal and broth Feedings should be offered frequently in small amounts as tolerated

For short term parenteral therapy give 100-150 grams carbohydrate in 5% solution per day If such feedings are required beyond a few days ensure 150 200 grams carbo-

hydrate plus protein—the National Research Council* advocates

Water	3000 cc	given as 2 liters
Casein hydrolysate	100 gms	5% casein hydrolysate
Glucose	200 gms	5% dextrose and
Salt	10 gms	1 liter 10% dextrose

To this one may also add parenteral vitamins

Special Dietary Problems—Peptic Ulcer

The co existence of peptic ulcer and diabetes poses a problem in dietary management which at first seems difficult and complicated, but actually it may be greatly simplified The same general plan of treatment for the ulcer in the diabetic patient is to be followed as in non diabetics provided certain special points are borne in mind The first is, the diabetic diet may not contain the highly concentrated carbohydrate foods such are often employed Extremely high fat and very low carbohydrate diets must be limited to only a few days or avoided entirely It is true that many diabetic patients, particularly those who have had diabetes for several years and who are thin, cannot take the high fat diets which result if a standard Sippy regime is employed Faithful adherence to a program of rest, frequent bland feedings, and control of the diabetic state are basically important

In the first few days and particularly following hemorrhages, hourly feedings of milk and cream may be employed In general with most diabetic patients, however, skim milk in amounts of one or two ounces every hour with addition of an ounce of cream in every third or fourth feeding will be found better than a plan which may provide a much higher fat diet The use of alkali may be the same as in non diabetics Within the next few days an addition of an egg, cooked cereal and a slice of bread may be made

* National Research Council on Convalescence and Rehabilitation, Report No 1, Feb 1944

in small amounts day by day Within a week or 10 days a modified convalescent diet might be employed such as is shown in Table 11 This diet list is a sample of the sort of

TABLE 11

DIET FOR DIABETES AND CONVALESCENT ULCER

Carbohydrate 153 Protein 75 Fat 99 Calories 1803

Diet

7 30 a.m. Milk and cream—4 ounces with breakfast

Breakfast	*Portions*	*Grams*
Cereal (cooked)	½ cup	120
Toast	1 slice	30
Butter	1 teasp	5
Egg	1	
Orange juice	small	100

(see list of substitutes opposite)

10 00 a m. Milk and cream—4 ounces

12 00 a.m Milk and cream—4 ounces with dinner

Dinner	*Portions*	*Grams*
Meat	3 ounces	90
5% vegetable	1 cup	150
10% vegetable	½ cup	75
Butter	1 teasp	5
Bread	1 slice	30
Orange juice	medium	150

(see list of substitutes opposite)

3 00 p m. Milk and cream—4 ounces

6 00 p m Milk and cream—4 ounces with supper

Supper	*Portions*	*Grams*
Cheese	1 ounce	30
or egg	1	
20% vegetable	½ cup	75
Bread	1 slice	30
Butter	1 teasp	5
Orange juice	medium	150

10 00 p m. Milk and cream—4 ounces

No smoking! No alcohol! Use tea & coffee

Avoid fried food gravies stews highly seasoned foods.

Do not take—pastry candy, nuts hot breads waffles pancakes raw fruits raw vegetables salad dressings carbonated drinks olives grapes bran buttermilk tomatoes corn, cabbage turnip cucumber

If stools are constipated dilute fruit juice with equal amount of hot water before breakfast If bowels do not move for 2 days take an enema

Substitution List

Milk and cream mixture must be milk 3 oz and 20% cream 1 oz If doctor advises calories may be increased to 2065 by using mixture of milk 2 oz and cream 2 oz

Cereal—must be one of the following cream of wheat oatmeal puffed rice, puffed wheat

Eggs—scrambled poached or soft-boiled

Bread—white graham fine rye (plain or toasted) Melba toast plain soda Uneeda or saltine crackers

Fruit—must be cooked or canned (waterpacked) No frozen fruits Strained fruit juices may be used

Fruits—in place of orange juice (100 gms) 3 prunes cooked without sugar (50 grams) or 1 cup of strawberries

Fruits—in place of medium orange (150 grams)

Blackberries	¾ cup	180 grams
Raspberries	¾ cup	120 grams
Blueberries	¾ cup	105 grams
Pear	medium	135 grams
Peaches	1½ medium	135 grams
Apricots	½ cup stewed	120 grams
or	2 ripe	

TABLE 11—Continued

Plums	3 medium	120 grams
Pineapple	½ cup or 2 slices	105 grams
Applesauce (without sugar)		105 grams
Cherries	13	90 grams
Prunes (stewed) (without sugar)	5	75 grams
Ice cream small serving		75 grams
Jello, medium serving		75 grams

Meat—may be fowl, chicken, turkey, broiled steak, lamb chops, roast beef or fish

Fish—broiled, boiled or baked white fish or hot boiled lobster, fresh crab or fresh shrimp

Cheese—American, cottage cheese, or Swiss cheese.

Vegetables—must be cooked and pureed Baby foods without sugar may be used

3%—summer squash, asparagus spinach, mushrooms, celery, cauliflower

8%—peas, string beans, carrots, winter squash, beets

20%—½ cup of macaroni ⅓ cup of rice, 75 grams (2½) ounces potato.

Potato—to be baked, boiled or riced.

dietary instruction given to a diabetic patient ready for discharge after a period of hospital treatment This diet as will be seen provides for carbohydrate 153, protein 75, and fat 99 grams—1803 calories It contains the prescribed amounts of food to be taken, not only in the three meals, but with four lunches with prohibitions of smoking and alcohol and instructions for substitutions

Liquid Diet

During emergencies due to fever or any condition which requires liquid feeding three plans are summarized in Table 12A. The first two diets are limited in calories, the third

TABLE 12A

Liquid Diets

Diet 1	*C 150*	P 50	*F 50*	*Calories 1250*
	1 quart of milk and 3 eggs 1 pint orange juice 1 pint ginger ale			
Diet 2	A glass of milk or fruit juice or ginger ale every 2 hours (7 feedings)			
Diet 3	C 158	P 64	F 104	Calories 1824
	Add to Diet No 1 another egg, 8 ounces of 20 per cent cream.			

intended for a patient able to take moderate amounts A liquid diet in four equal meals providing a total of carbo-

Diet 4

TABLE [illegible]

(*Carb 188 gm Protein 108 gm Fat 67 gm*)
1787 Calories

No Exchanges	*Food Exchange*	*List No*	*Sample Menu*	*Household Meas*	*Wt Gm*	*C*	*P*	*F*	*Cal.*
6·00 A M									
1	Bread	4	Oatmeal in	½ c	20	15	2	—	68
1	Milk	1	Milk whole	1 c	240	12	8	10	170
2	Meat	5	Eggs coddled	2	—		14	10	146
1½	Fruit	3	Pineapple juice	½ c	120	15	—	—	60
				Total		42	21	20	444
12·00 Noon (Repeat at 6·00 P M with suitable exchanges)									
			Soup (thin with broth)						
2	Meat	5	Meat purée	2 oz	60	—	14	6	110
1	Bread	4	Potato mashed	½ c	100	15	2	—	68
1	Vegetable	2B	Peas purée	½ c	100	7	2	—	36
1½	Fruit	3	Grapefruit juice	¾ c	150	15	0	0	60
1	Milk	1	Milk whole	1 c	240	12	8	10	170
				Total		49	26	16	888
12·00 Midnight			Milk drink						
2⅔	Milk	1	Milk skim	1 pt	480	21	16	—	160
	Milk	1	Milk skim powder	1 tbsp	12	4	2	—	21
2	Meat	5	Eggs	2	—	—	14	10	146
1	Fat	6	Light cream	2 tbsp	30	—	—	5	45
2	Fruit	3	Grape juice	½ c	120	20	—	—	80
				Total		*48*	*32*	*15*	*455*
				Day's Total		188	108	67	1787

This liquid diet is designed for patients with acute complications and who are unable to eat regular food The division into 4 equal meals one every 6 hours in conjunction with 4 doses of regular insulin facilitates the control of the diabetes during emergency periods

hydrate 188 grams with 1787 calories is shown in the fourth diet

TABLE 13

SALT FREE DIET (C 119 P 46, F 38 Cal 1002)

Weight in Grams	Food	C	P	F	Na grams
Breakfast					
100	Orange Juice (½ cup scant)	10			.010
50	Egg (one) Do not use bacon		6	6	.070
100	Oatmeal or Farina (½ cup scant)	10	2 5	1	.071
100	Milk (½ cup scant)	6	4	4	.051
5	Salt Free butter (1 tsp)			4	.005
					.207
Dinner					
50	Meat (1½ oz small serving. No ham or salted meats No fish)		12	7 5	053
100	Potato (large)	21	3 5		024
50	Vegetables (½ cup, see list)	3	1		039
150	Orange (see list)	15			016
5	Salt free butter (1 tsp)			4	005
					137
Supper	Same as dinner	39	16 5	11 5	137
Bedtime	150 Orange (see list)	15			015

Vegetables Fresh or Frozen

You may have 50 grams of any vegetable on this list

Asparagus
Carrots
String beans
Beets
Broccoli
Cabbage
Cauliflower
Lettuce
Onions
Peas
Squash
Tomatoes
Tomato Juice (without added salt)
Turnip

Fruits

You may have any fruit on this list in the amount shown in place of 150 gms orange

100 Apple (1 very small)
100 Blueberries (¾ cup)
100 Cherries (13 cherries)
150 Orange (1 medium)
135 Pears (1 medium)
100 Pineapple (2 slices)
120 Raspberries (¾ cup)
225 Strawberries (1½ cups)
225 Grapefruit (1 medium)

* *All foods must be cooked without any salt Do not use any salt at the table.*

Diets Restricted in Salt

For many diabetic patients during periods of cardiac failure, particularly during certain stages of diabetic nephropathy, marked salt restriction becomes necessary Table 13 has shown a salt poor diet which provides for carbohydrate 119, protein 46 and fat 38 grams with 1002 calories This diet is intended for a patient confined to bed When *activity is increased such a diet might be increased by the* addition of meat, cream and vegetables to caloric levels indicated

In Table 14 are given standard diets First, providing for carbohydrate 157, calories 1669, second, providing for carbohydrate 169, calories 1899

Appendix

Mineral, Vitamin, Calorie Requirement

In Table 15 are summarized the recommended daily dietary allowances of the Food and Nutrition Board of the National Research Council

TABLE 14

NAME DATE

Breakfast Insulin ______ Units	Grams	Portions	Dinner Insulin ______ Units	Grams	Portions	Supper Insulin ______ Units	Grams	Portions	Total Daily Diet C 157 – P 69 – F 85 – Cal 1669	C – P – F Grams
Eggs		1	Eggs			Eggs			Eggs	0 – 6 – 6
Meat cooked			Meat cooked	60	2 oz	Meat cooked	60	2 oz	Meat cooked	0 – 28 – 20
Bacon			Bacon			Bacon			Bacon	
3% Veg			3% Veg	150	1 cup	3% Veg	150	1 cup	3% Veg	20 – 5 – 0
6% Veg			5% Veg	75	½ cup	6% Veg	75	½ cup	6% Veg	
Oat dry	(15)		Oat dry			Oat dry			Oat dry	
Oat cooked	120	½ cup	Oat cooked			Oat cooked			Oat cooked	10 – 3 – 1
Crackers			Crackers			Crackers			Crackers	20 – 3 – 2
Butter	5	1 tsp	Butter	10	2 tsp	Butter	10	2 tsp	Butter	0 – 0 – 20
Cream 20%	60	2 oz	Cream 20%	30	2 tbsp	Cream 20%	30	2 tbsp	Cream 20%	4 – 4 – 24
Milk	120	½ cup	Milk			Milk			Milk	13 – 12 – 12
Orange*	100	Small	Orange*	150	Medium	Orange*	150	Medium	Orange*	40 – 0 – 0
Cheese			Cheese			Cheese			Cheese	
Potato			Potato			Potato			Potato	
Bread	30	1 slice	Bread	30	1 slice	Bread	30	1 slice	Bread	45 – 8 – 0

BETWEEN MEAL FEEDINGS Forenoon 2 Crackers Afternoon 2 Crackers, Milk (½ cup) Bedtime 2 Crackers, Milk (½ cup)

Tea coffee and clear broths may be used as desired Meat means your choice of meat fish poultry or cheese.
* Orange or equivalent of fresh or water-packed fruit
If cream butter and crackers were omitted the above diet would be C 133 P 62 F 39 Calories 1181

TABLE 14—Continued

NAME DATE

Breakfast			Dinner			Supper			Total Daily Diet	
Crys Insul n______Units NPH Insul n______Units			Crys Insul n______Units			Crys Insulin______Units			C 169 – P 83 – P 99 – Cal 1899	
	Grams	Portions		Grams	Portions		Grams	Portions		Grams
Eggs		1	Eggs			Eggs			Eggs	
Meat cooked			Meat cooked	75	2½ oz	Meat, cooked	75	2½ oz	Meat cooked	
Bacon	15	2 strips	Bacon			Bacon			Bacon	
6% Veg			3% Veg	150	1 cup	3% Veg	150	1 cup	3% Veg	
10% Veg			6% Veg	75	½ cup	6% Veg	75	½ cup	6% Veg	
Oat dry	(15)		Oat dry			Oat dry			Oat dry	
Oat cooked	120	½ cup	Oat cooked			Oat cooked			Oat cooked	
Uneedas			Uneedas			Uneedas			Uneedas	
Butter	10	2 tsp	Butter	10	2 tsp	Butter	10	2 tsp	Butter	
Cream 20%	60	¼ cup	Cream 20%	30	2 tbsp	Cream 20%	30	2 tbsp	Cream, 20%	
Milk	120	½ cup	Milk			Milk			Milk	
Orange	100	Small	Orange	150	Medium	Orange	150	Medium	Orange	
Cheese			Cheese			Cheese			Cheese	
Potato			Potato			Potato	90	3 oz	Potato	
Bread	30	1 slice	Bread	30	1 slice	Bread	30	1 slice	Bread	

3 p m "2 Uneedas 120 Milk" (½ cup) Bedtime 2 Uneedas

TABLE 15—RECOMMENDED DAILY DIETARY ALLOWANCES, REVISED 1948

(Food and Nutrition Board, National Research Council)

	Calories[1]	Protein (gm)	Calcium (gm)	Iron (mg)	Vitamin A[2] (I U)	Thiamine[3] (mg)	Riboflavin[3] (mg)	Niacin (Nicotinic Acid)[3] (mg)	Ascorbic Acid (mg)	Vitamin D (I U)
Man (154 lb, 70 kg)										
Sedentary	2400	70	1 0	12[4]	5000	1 2	1 8	12	75	[5]
Physically active	3000	70	1 0	12[4]	5000	1 5	1 8	15	75	[5]
With heavy work	4500	70	1 0	12[4]	5000	1 8	1 8	18	75	[5]
Woman (123 lb, 56 kg)										
Sedentary	2000	60	1 0	12	5000	1 0	1 5	10	70	[5]
Moderately active	2400	60	1 0	12	5000	1 2	1 5	12	70	[5]
Very active	3000	60	1 0	12	5000	1 5	1 5	15	70	[5]
Pregnancy (latter half)	2400[6]	85	1 5	15	6000	1 5	2 5	15	100	400
Lactation	3000	100	2 0	15	8000	1 5	3 0	15	150	400
Children up to 12 yrs[7]										
Under 1 yr[8]	110/2 2 lb (1 kg)	3 5/2 2 lb (1 kg)	1 0	6	1500	0 4	0 6	4	30	400
1 3 yrs (27 lb, 12 kg)	1200	40	1 0	7	2000	0 6	0 9	6	35	400
4-6 yrs (42 lb, 19 kg)	1600	50	1 0	8	2500	0 8	1 2	8	50	400
7 9 yrs (58 lb 26 kg)	2000	60	1 0	10	3500	1 0	1 5	10	60	400
10-12 yrs (78 lb, 35 kg)	2500	70	1 2	12	4500	1 2	1 8	12	75	400
Children over 12 yrs[7]										
Girls 13-15 yrs (108 lb, 49 kg)	2600	80	1 3	15	5000	1 3	2 0	13	80	400
16-20 yrs (122 lb 55 kg)	2400	75	1 0	15	5000	1 2	1 8	12	80	400
Boys 13-15 yrs (108 lb, 49 kg)	3200	85	1 4	15	5000	1 5	2 0	15	90	400
16-20 yrs (141 lb, 64 kg)	3800	100	1 4	15	6000	1 7	2 5	17	100	400

[1] Calorie allowances must be adjusted up or down to meet specific needs The calorie values in the table are therefore not applicable to all individuals, but rather represent group averages The proper calorie allowance is that which over an extended period will maintain body weight or rate of growth at the level most conducive to well being

[2] The allowance depends on the relative amounts of vitamin A and carotene The allowances of the table are based on the premise that approximately two-thirds of the vitamin A value of the average diet in *this country is contributed by carotene* and that carotene has half or less than half the value of vitamin A

[3] For adults (except pregnant and lactating women) receiving diets supplying 2000 calories or less such as reducing diets, the allowances of thiamine and niacin may be 1 mg and 10 mg respectively The fact that figures are given for different calorie levels for thiamine and niacin does not imply that we can estimate the requirement of these factors within 500 calories, but they are added merely for simplicity of calculation In the present revision, riboflavin allowances are based on body weight rather than calorie levels Other members of the B complex also are required, though no values can be given Foods supplying adequate thiamine, riboflavin and niacin will tend to supply sufficient of the remaining B vitamins

[4] There is evidence that the male adult needs relatively little iron The need will usually be provided for if the diet is satisfactory in other respects

[5] The need for supplemental vitamin D by vigorous adults leading a normal life seems to be minimum For persons working at night and for nuns and others whose habits shield them from the sunlight, as well as for elderly persons, the ingestion of small amounts of vitamin D is desirable

[6] During the latter part of pregnancy the calorie allowance should increase to approximately 20 per cent above the preceding level The value of 2400 calories represents the allowance for pregnant, sedentary women

[7] Allowances for children are based on the needs for the middle year in each group (as, 2, 5, 8 etc) and are for moderate activity and for average weight at the middle year of the age group

[8] Needs for infants increase from month to month with size and activity The amounts given are for approximately 6 to 8 *months* The *dietary requirements for* some of the nutrients such as protein and calcium are less if derived largely from human milk.

CHAPTER III

INSULIN

General Considerations

That the prime objective in the treatment of diabetes is the removal of all the signs and symptoms of diabetes, has been repeatedly stated by Professor Charles H Best, the co discoverer with F G Banting of insulin This is certainly the simplest definition of the control of diabetes Is it necessary to avoid hyperglycemia and glycosuria? Although arguments have been advanced pro and con available evidence today favors preponderately the maintenance of the diabetic patient's blood chemistry within normal limits Not only, therefore, is it desirable that the blood sugar should be maintained as nearly normal as possible under all conditions but other chemical components of the body tissues, which are in our present state of knowledge regarded as bearing a direct relationship to intracellular metabolic changes, should also be studied These include cholesterol, the other plasma lipids, blood proteins and serum electrolytes

In recent years, much emphasis has been placed upon the function of the liver in diabetes and today the importance of maintaining normal glycogen storage is generally accepted Any factors which deplete glycogen storage in the liver such as insulin lack, hyperthyroidism, infection, hepatitis, starvation, surgical procedures, anesthesia, vomiting, will result in an increased fat utilization with the production of excessive amounts of acetone On the contrary when glycogen storage is maintained through the interaction of many

factors chief of which in the diabetic is insulin the patient s liver is better protected

The protection of the insulin producing function of the islet cells of the pancreas is aided by the use of insulin It has been shown that hyperglycemia itself is a major factor in animals in *producing degenerative changes in islet cells* and therefore the basic rule in treatment today is to give sufficient insulin to control hyperglycemia and so protect the islands of Langerhans

Insulin Action

Insulin is an aqueous solution of the active antidiabetic principle derived from the islands of Langerhans in the pancreas When a diabetic is given insulin in appropriate doses and under proper conditions he is enabled to utilize carbohydrates and fats in a comparatively normal manner The concentration of sugar in the blood is confined within normal limits The urine remains free of sugar and ketone bodies and diabetic acidosis and coma are prevented The effect of a dose ordinarily lasts from five to eight hours or more depending upon such factors as the size of the dose the diet and the amount of exercise during that period In directly insulin in the diabetic patient affects protein metabolism and insulin has recently been shown to be essential for the action of the growth hormone Major effects of in sulin are the transformation of carbohydrate into fat and the prevention of excessive ketone formation

When Abel first prepared crystalline insulin (1926) no physiologically active pure protein was known Today the insulin molecule is known to be composed of 17 amino acids

Current concepts of the mode of action of insulin are five in number

1 The transfer mechanism assumes that insulin acts by facilitating the transportation of glucose through cell membranes The evidence adduced by Levine et al. suggests

that insulin promotes the transfer of glucose across cell membranes Once inside the cell, glucose would be processed by the accepted pathways

2 The hexo kinase theory proposes that insulin acts on the enzyme hexo kinase, accelerating conversion of ... to glucose hexosepho... hibition of

3 As ... this theory relates the rôle of insulin to the production of high energy phosphate bonds needed for all synthetic reactions Thus, the high oxygen consumption of the untreated mildly acidotic diabetic in the old era before insulin stands in striking contrast to the more efficient metabolism of the controlled diabetic under insulin treatment

4 The rôle of insulin is to inhibit the phosphatase system

5 Insulin affects the synthesis of fatty acids

In the early preparation of insulin it was apparent that it contained some measure of a hyperglycemic factor, presumably formed in the alpha cells of the islands of Langerhans In recent years this substance has been isolated in pure form and identified as glucagon At present glucagon has no practical application in treatment

A number of insulin preparations have been made during the last twenty years, all of which possess the same basic property of insulin in its effect upon carbohydrate metabolism Each of these preparations, however, differs from the others in some respect both in composition and in the character of its effect on the patient At present no insulin preparation can be taken by mouth with clinical effect, owing to the fact that the insulin molecule is broken down in the intestinal tract by the powerful proteolytic enzymes of the pancreas Many attempts have been made, by reducing the size of the molecule in order to obtain the most effective portion, to find a molecule which would so rapidly

penetrate the intestinal mucosa as to make absorption too rapid for its destruction to occur

Only regular insulin and crystalline insulin can be given, intravenously, the method of choice in securing the most active effect in such emergencies as diabetic coma All other insulins must be given hypodermically The following table briefly summarizes differences in the rate of action

TABLE 16

INSULIN ACTIVITY

Type of Insulin	*Onset of Action*	*Peak of Action*	*Duration of Action*
Regular	1 hour	3-4 hours	6-8 hours
Crystalline	1 hour	3-4 hours	8-10 hours
Globin	1 hour	8-10 hours	18-24 hours
Protamine zinc	4-8 hours	20-24 hours	24-48 hours
NPH	2 hours	8-10 hours	24-30 hours
Lente	1 2 hours	8-10 hours	24-30 hours
2 1 Mixture Crystalline and PZI	2-4 hours	8-10 hours	24-30 hours

Factors which will increase the hypoglycemic effects of insulin of all varieties include underactivity of the anterior pituitary, the thyroid and the adrenal cortex, undernutri tion, low carbohydrate intake, exercise The effect of insulin upon the blood sugar level is decreased by overactivity of the pituitary, thyroid and adrenal cortex, obesity, high carbohydrate intake, and high caloric diets and lack of muscular activity, infections, diabetic acidosis and excessive stress

Regular Insulin and Insulin Made from Zinc Insulin Crystals

Insulin made from zinc-insulin crystals is the solution from the crystalline preparation containing insulin together with a small amount of zinc Such crystals are typical of the only form in which insulin has been prepared in a pure crystalline state This insulin has the advantage of being so

pure as to be especially indicated in patients who show an allergic reaction to regular insulin Insulin made from either crystalline or non crystalline sources is rapidly absorbed and acts quickly and intensively for a few hours

Insulin is measured in units and can be purchased in concentrations containing commonly 40 to 80 units per cc Concentration of 10 and 20 units per cc, originally manu factured, should seldom if ever be prescribed One unit, on the average, is usually said to metabolize one to four grams of sugar However, much variation will occur even in the same individual at different times under varying conditions, such as presence of infection, variations in diet variations in electrolytes, presence of acidosis, and other circumstances Each of these two insulins has been sold as a water clear acid solution

Globin insulin, a clear, slightly amber solution with an acid pH resembles NPH insulin in its rate of action and its effect It acts a little more rapidly and perhaps has caused more reactions at the period from 3 until 5 in the afternoon Although Globin insulin is clear, it may not be given in travenously

Lente Insulin, now available commercially in the United States, has a duration of action which in most patients is about 25 hours and is similar in its action to NPH (Iso phane) insulin The prolonged action of previous insulin compounds has been attained by the addition of basic protein substances, such as protamine, globin or histone together with a small amount of zinc Those compounds are insoluble at the pH of blood In the preparation of these insulins, a phosphate buffer was commonly used Hallas Moller and his associates showed that if acetate was sub stituted as the buffer for phosphate or citrate, zinc in low concentration combined with insulin to form compounds that at the pH of the blood are relatively insoluble Three types of insulin zinc suspensions were made, insulin semi lente, a preparation with duration of action of 12 14 hours

insulin ultralente, a crystalline compound with action lasting more than thirty hours, and insulin Lente, a mixture of ultralente and semilente The present Lente insulin is similar to this latter type A comparison of Lente insulin with NPH insulin shows that they have duration of action of about 25 hours and the two types may, in general, be used interchangeably Crystalline insulin may be given in a single injection mixed with Lente insulin just as with NPH insulin A *few patients, particularly children, complain of* discomfort at the site of injection of Lente insulin Allergy to Lente insulin does occur, but at present, experience suggests that it is not so frequent as with other forms of insulin.

CHAPTER IV

USE OF INSULIN IN TREATMENT

Indications

The indications for the use of insulin may be in the interest of brevity stated as follows (1) Always in diabetic children (2) Almost always during complications such as infections, surgery and delivery (3) Always in the presence of diabetic acidosis or coma (4) All patients with constant hyperglycemia, glycosuria or other symptoms of active diabetes

When the diabetes has come under control, improvement in tolerance will be followed by a reduction in the dose of insulin and in many cases with diabetes in the latter part of life insulin may be omitted provided the patients can maintain normal weight and strength without hyperglycemia and glycosuria Rapid reduction of weight in the obese mild diabetic patient may bring the diabetes under control without continuous use of insulin In many patients it is desirable to continue the use of insulin even at intervals of 48 hours instead of 24 hours rather than to run the risk of an allergic reaction to insulin months or years later when the patient, whose insulin has been omitted, must under the stress of surgical emergencies, infections or other causes have immediate treatment with moderately large doses of insulin

The foundation or basic insulin in most cases is today one of the insulins with prolonged action, such as NPH insulin, Lente insulin, protamine zinc insulin or Globin insulin Un

modified insulin, either regular or crystalline insulin is commonly used as an additional or supplementary dose when a quick and powerful action is needed This is particularly true in emergencies and during complications and in certain labile patients in whom the requirement of insulin changes rapidly Regular or crystalline insulin will be able to balance exogenous carbohydrate while protamine zinc insulin is much slower than crystalline zinc insulin in controlling considerable amounts of carbohydrate taken by mouth Protamine zinc insulin, therefore, does not protect the patient against hyperglycemia and glycosuria occurring especially after meals A single dose of protamine zinc insulin will in a fasting person produce a steady decline in the blood sugar level However, when the effect of three meals is added, the hyperglycemia is frequently not controlled The blood sugar level may be low in the fasting state but it is higher after breakfast and lunch because protamine zinc insulin releases slowly Protamine zinc acts longer than 24 hours, and therefore the patient may have on the second day the effects of the dose taken 24 hours previously and the dose taken on that morning This overlapping effect is the important feature of protamine zinc insulin

Our experience has been that patients who have mild or moderate diabetes, particularly in middle life, usually do well with protamine zinc insulin alone provided their insulin requirement is not more than 20 to 30 units However, in severe cases requiring larger doses usually protamine zinc insulin requires supplementary doses of regular insulin

The use of mixtures of regular or crystalline insulin and protamine zinc insulin to obtain an intermediate effect is justified in patients requiring 40 units or more daily and in patients who would otherwise require multiple injections The mixture of two parts quick acting insulin and one part protamine zinc insulin can be made by the patient or the doctor and is now available However, at present NPH in-

sulin, Lente insulin or Globin insulin as well as the mixture are sufficiently powerful to cover the postprandial hyperglycemia of the daytime

Immediate use of insulin is urged in early cases of diabetes with glycosuria and hyperglycemia in order to protect the pancreas and to improve carbohydrate tolerance as rapidly as possible It is urgently needed in patients who are obviously sick and suffering from typical diabetic symptoms of thirst, dehydration and loss of weight It is always needed in the presence of ketosis and usually in the intercurrent complicated disease, sepsis, gangrene or hyperthyroidism

We prefer to use insulin immediately in patients who come to the office with newly discovered glycosuria and hyperglycemia, or even in old patients who come in with such unregulated diabetes even though they have gone on for years without any Unless one immediately begins the use of insulin, the patient does not realize that the doctor is taking his condition seriously If the condition is really serious, then in the patient s mind insulin should be begun If the doctor delays, it means either that the doctor is un certain or else that the condition is not really as urgent as it seems Today it is obvious that one of the important rea sons *for the failure to control diabetes* and the failure of patients to take their condition and its treatment more seriously is the fact that in the early stages of diabetes doc-*tors are prone to minimize the seriousness* of the condition in order to reassure the patient Actually, diabetic patients need to learn soon after the onset that diabetes is a serious, *chronic disease which is not going* to be terminated like a cold in the head or some other acute illness, secondly, its treatment is for life, thirdly, that if treatment is carried on *faithfully, improvement can be expected* Many adult pa tients without any symptoms such as loss of weight, polyuria or ocular complications in whom the diagnosis has been *made only by the finding* of hyperglycemia and glycosuria under stress, as for example in a glucose tolerance test or

in a test of blood sugar one hour after breakfast, may be treated without insulin for long periods Nevertheless, they should never be told that they have been cured They should understand from the onset that continued medical observation is essential and that blood sugar and urine tests should be done one hour after a meal at least once a year If such patients do not continue to be under control with normal or nearly normal blood tests, then the use of insulin should be begun If the urine does not become sugar free soon after the inauguration of dietary treatment, the diet will need within 48 hours further reduction in caloric intake and carbohydrate content or the use of insulin should be begun

Whatever may be the plan of treatment with regard to the use of insulin, the patient should collect the urine each day and *bring it or send it in for examination* Usually we instruct patients to test the urine before each meal and then save the urine in a 24 hour amount Sometimes the 24 hour amount is not collected rigidly in patients who are undergoing treatment at home, but it is an absolute rule in the New England Deaconess Hospital that all patients with diabetes or suspected of having diabetes shall have a 24 hour urine amount collected each day, the sugar tested and quantitated so that the percentage of sugar excreted is known and the total amount of sugar in grams is charted In many patients, the urine will not become sugar free with the small initial doses of perhaps 5-10 units of NPH insulin which are used In that event, each day the insulin dose may be increased by 5 units In some patients in whom the urine tests before each meal continue to show large amounts of sugar, small doses of NPH or Lente insulin can be given before the evening meal as well as before the breakfast meal It is important to realize that some diabetic *patients* may be sensitive to insulin at the onset of treatment It is extremely important to realize that small children, 1-5 years of age, may be so sensitive that insulin should

rarely be given in more than 5 or 10 units at a time Indeed as a working rule, 5 units at 1 year of age, 10 units at 5 years of age, and 20 units at 10 years of age in newly discovered diabetes without ketosis is safe Serious hypoglycemia may be produced if such small children are given doses of 20, 30 or 40 units at a time On the other hand in patients with diabetes of long standing who prove to be resistant to insulin, either because of accompanying infections, obesity, or the long duration of severe diabetes, the dose which may have been begun with 5 or 10 units may need within 24 hours rapidly to be increased to 25, 50 or 100 units Here it is that the close following of every urine specimen and constant watching of the patient is of basic importance

On the first visit when insulin is to be used, the patient must be instructed by the office nurse or an office secretary, who has received special training in these techniques, to use insulin Ordinarily, the patient is instructed to obtain a vial of insulin of U40 concentration The appropriate syringes are graduated in units or fractions of a cubic centimeter At present, the so called American Diabetes Association syringes are much used The patient requires cotton and a bottle of Iso propyl alcohol When convenient, the first few doses of insulin may well be administered by the doctor himself or an office nurse As soon as possible the patient or a member of his household, preferably both should learn to measure the dose in units and to give the injection with special care for cleanliness, asepsis and the avoidance of frequent injections in the same area In Table 17 are given directions which we give to patients at the Deaconess Hospital and at our office

Dosage

Mild diabetics may frequently be controlled with a single dose of insulin given before breakfast Although treatment may be begun with small doses of 5 units, it may

be increased 3-5 units every day or two and some patients may require a second dose before supper or a rapidly increased dosage Thus, patients who have glycosuria in all specimens must have their insulin dose steadily increased 5-10 units at a dose until in the first few days they may be taking as much as 10 20 units three times a day Usually by that time, the situation may have changed so that the patient who has been taking 20 units of NPH or Lente insulin before breakfast will now be found to be sugar free in the afternoon and the evening dose can be omitted Within a few days thereafter, the noon dose may also be omitted, particularly if one adds to the morning dose of Lente insulin or NPH insulin a mixture of 5-10 units of regular insulin

TABLE 17

Instructions to the Patient for Giving Insulin Subcutaneously

1 *Sterilization* Wash the hands thoroughly with soap and water Place the cylinder and piston of the syringe separately the needle and an empty 4 ounce bottle or a covered dish on a clean piece of cloth in the bottom of a pan Cover completely with cold water heat to boiling and let boil for 5 minutes Pour off the water, being careful not to touch anything in dish, and allow to cool by standing Then place bottle or dish on table and fill with iso-propyl alcohol Pick up cylinder of syringe Pick up piston carefully by knob at extreme end and put into cylinder Pick up needle by butt and place on syringe, pressing down hard and turning a little to left or right to insure tightness Then place syringe with needle attached into 4 ounce bottle of alcohol or cover the syringe and needles unattached in the dish with alcohol

[illegible] two weeks

[illegible] ll of alcohol

[illegible] of alcohol by pulling piston back and forth

Paint the top of the insulin bottle with alcohol

2 *Loading* Draw the piston so that the syringe contains as much air as the amount of insulin needed.

Push the needle cautiously but firmly through the exact center of the rubber cap push the piston down expelling air into the bottle invert the bottle then withdraw as much insulin as desired If air bubbles are present holding syringe and needle point upward, expel insulin into bottle and slowly again withdraw the desired amount

3 *Injection* Use right leg or arm one day and left the next day Divide skin of thighs and arms into four rows Inject along these at one inch intervals using the same point not more often than once a month

Having decided on the site for injection, starting in the center in a circular motion clean gently an area as large as a 25 cent piece with iso propyl or rubbing alcohol

Pick up a fold of the skin between the thumb and forefinger of the left hand and with the syringe held at a forty five degree angle to the skin push the needle quickly and firmly crosswise into the fold nearly up to the butt Then release the fold and steady the needle by its butt

Force the insulin gradually out of the syringe with thumb Cover area of injection with alcohol sponge Pull out needle Again wash off

If the insulin has been given too close to the upper layers of the skin a white blister like elevation will appear

4 *Cleaning up* Rinse the syringe and needle in the alcohol in the 4 ounce bottle by pulling alcohol up into cylinder of syringe at least two times Leave in alcohol ready for next injection of insulin If covered dish is used rinse syringe and needles with cold water before placing in dish

Methods of Management

Protamine Zinc Insulin

The best time for the administration of protamine zinc insulin is before breakfast in the morning This is true whether the injection is accompanied by the use of regular or unmodified insulin or not Careful observation of the patient with laboratory tests of blood sugar levels should be secured It is important to remember that with protamine zinc insulin a period of several days may pass before the full effect of protamine zinc insulin is obtained This is in part due to the prolonged action of protamine zinc insulin and the overlapping of one day s dose with that of the next During the period of adjustment to protamine zinc insulin

usually supplementary doses of regular insulin at noon or before supper may be necessary if the glycosuria is to be brought under control If doses of protamine insulin are increased too rapidly it is easy to produce serious hypoglycemia It should be emphasized repeatedly that in many patients particularly those who have been using regular insulin for a period of years the time required for best results with protamine zinc insulin may be prolonged from a few weeks to several months

In some severe patients the injection of regular or unmodified insulin is necessary before the evening meal or at bedtime to prevent excessive rises in blood sugar levels during the late night When protamine zinc insulin is given before supper or in the evening a small dose is required approximately equal to the number of units of regular insulin which might be given at that time If glycosuria continues the dose may have to be increased This method of giving protamine zinc insulin twice a day has been very rarely used in this clinic

Protamine zinc insulin is effective in beginning the treatment of new cases of uncomplicated diabetes A dose of 10 units which is to be increased by 5 or 10 units each day or so is commonly employed The dose may be increased each day until the total reaches 30 or 40 units If glycosuria persists particularly after meals a separate injection of regular insulin may be given before breakfast at the same time as protamine insulin beginning at 5 units and increasing perhaps by 3-5 units each day It is seldom necessary to give supplementary doses of more than 20 units or with protamine zinc insulin exceeding 50 units When the protamine zinc insulin dose exceeds 50 units it usually is advantageous to give a supplementary dose of regular insulin at the same time in the morning

In cases previously treated with insulin for long periods the substitution for protamine zinc insulin may be made by giving one daily injection of protamine zinc insulin equal

to about four fifths of the total number of units previously required in three or four injections If glycosuria persists in the late morning or early afternoon changing the exercise or food intake may be indicated Better still a supplementary dose of 5 10 units of unmodified insulin may be added Again the dose of protamine insulin is regulated with the amount of sugar in the urine obtained upon rising in the morning or, better still, the second specimen one-half hour later or by the blood sugar test In contrast the dose of unmodified or regular insulin is usually adjusted according to the amount of sugar in the late morning or early afternoon specimen

The amount of protamine zinc insulin required is usually about two thirds the number of units of the patient s former daily dose of regular insulin In the first few days of change it may be necessary to continue small doses of the regular insulin until the more prolonged action of protamine zinc insulin has become well established

Insulin and Protamine Zinc Mixtures

The majority of adult diabetic patients of short duration can be controlled by unmodified insulin if enough doses are given or by single doses of protamine zinc insulin if the total insulin requirement is less than 30-50 units a day Various types of dietary planning have been used in adjusting patients of the group who have more severe types of diabetes Mixtures of regular and protamine zinc insulin really permit a more specialized and individualized treatment of each case since the patient may make such mixtures as are suitable to his own changing condition These extemporaneous mixtures by earlier reporters soon after the administration of protamine zinc insulin began have been employed pretty generally In the Joslin Clinic, such mixtures have been less and less used particularly since the introduction of NPH insulin and now of Lente insulin One

difficulty with the mixture of insulins is that for some patients no longer young, with eyesight which is not acute, and with hands used to heavy manual labor, it is easy to make errors The technique for mixing must be very carefully explained individually to the patient Suppose the dose is to be 40 units of regular insulin and 20 units of protamine zinc insulin (2 1 mixture) This total of 60 units might be made from either U40 or U80 insulin and from protamine zinc insulin containing either U40 or U80 strength It is better to use one concentration rather than confusing the patient with two different strengths of insulin More and more U80 strength insulin is being employed When possible the bulk of the dosage should be reduced to 1 cc or less First draw the clear insulin up to the 40 unit mark and then pull the plunger back so that with the needle pointing upward there is as much air above the clear insulin as is equivalent to the units of protamine zinc insulin to complete the dose Then, insert the needle into the rubber cork of the protamine zinc insulin bottle and force the air into the bottle Then withdraw the 20 units of protamine zinc insulin needed It is important to always withdraw clear insulin first because it will not matter if a little clear insulin enters the vial of protamine zinc insulin If, on the other hand, a small amount of protamine zinc insulin gets into the vial of regular insulin, it will cause the clear insulin to become cloudy The practice with two used insulin vials and under the coaching and observation of a nurse, will increase the patient's confidence and his accuracy in this technique

Dietary Adjustments

When using protamine zinc insulin regulation of the diet is a factor of fundamental importance Differences, however, are inherent in the use of protamine zinc insulin [illegible] of the fact that protamine zinc insulin cannot [illegible] peak carbohydrate load of diabetic diet, [illegible]

the meals come fairly close together Difficulty may not be marked in mild patients, but in more severe diabetic patients adjustments in the diet may be necessary before rearrangement accomplishes good control Protamine zinc insulin is more continuous in its action than regular insulin Following injection of protamine insulin the carbohydrate in the meals should be reduced somewhat Thus, the amount of carbohydrate in the breakfast may be reduced to one fifth or even one sixth of the total carbohydrate of the day Carbohydrate for lunch may be two fifths of the total and of this two fifths, perhaps 10 15 grams should be given in the form of a lunch at 10 30 or 11 30 a m Similarly, the supper carbohydrate may be two fifths of the total and should include a bedtime lunch of perhaps 10-20 grams of carbohydrate Often this bedtime lunch should include the protein in the form of cheese, since the protein breakdown which yields carbohydrate is more gradual and there is, accordingly, better protection against hypoglycemia during the later hours of the night Methods for adjusting the diet may be found on pages 57 64

Every case must be treated individually with particular regard for the changing hours of work of the patient and particularly for the amount of muscular exercise necessary A sugar free urine specimen before breakfast accompanied by a normal blood sugar level is the objective It makes unnecessary any increase in the dose of protamine zinc insulin and usually will require a slight reduction in that dose particularly if the urine continues sugar free after the second or third day Hypoglycemia clearly indicates the need for revising the dose or the diet

Methods of Management of NPH Insulin

NPH insulin is best injected before breakfast in the morning again with consideration for individual management and planning In most instances, a period of observa

tion with laboratory tests including blood sugar and urine examinations will be necessary before successful adjustment of the blood sugar level can be accomplished The amount of insulin dosage, time of injection and the diet and exercise will require direct, continuous medical supervision

In the new uncomplicated case, the dose of NPH insulin may be 10 15 units before breakfast in the morning for adults However, as with all types of insulin it should be remembered that small children under 5 years of age are extremely sensitive to insulin and usually dosages in their cases will be 3-5 units unless ketosis is present The patient already being treated with protamine zinc insulin or unmodified insulin, one may begin with a dose containing fewer total units than had been required Usually reduction of approximately 10 per cent has been found successful It is easy to substitute NPH insulin for the 2 1 mixture of insulin and protamine zinc insulin since the activity of NPH insulin really closely resembles such a mixture Exchanging unit for unit is usually effective and no particular alteration of the diet or general management is needed

Frequently, in some severe patients an addition to NPH insulin of quick acting insulin will be required Fortunately, NPH insulin because of its crystalline composition does not combine readily with added unmodified insulin and, therefore, a mixture of NPH insulin with regular insulin has the same activity as if the two doses had been injected separately With NPH insulin as with any insulin preparation, the regulation of diet is of basic importance Each case must be treated individually and the effect of diet, exercise and infections on the dosage required will need careful study In certain severe cases, there may be an advantage in prescribing a smaller breakfast and larger noon meal just as is done with protamine zinc insulin and globin insulin In such instances the distribution of carbohydrate food is usually $\frac{1}{5}$, $\frac{2}{5}$, and $\frac{2}{5}$

Lente Insulin

Lente insulin, now available commercially in the Unitec States, has a duration of action which in most patients i about 24 hours and is similar in its action to NPH, Isophane insulin

CHAPTER V

HYPOGLYCEMIA DUE TO THE ADMINISTRATION OF INSULIN

Hypoglycemia due to the administration of insulin is of great concern to students of diabetes In childhood it can lead to failure in school social embarrassment and interference with athletic progress In adult life it can restrict choices of occupation, require change of occupation lessen manual skill, alter judgment Eventually it can lead to loss of money, prestige or even to social disgrace Rarely it leads to death In their efforts to avoid the sequelae of hypoglycemia diabetic patients tend to follow suboptimal insulin treatment

(a) *Physiology*

Hypoglycemia is the physiological end result of an important action of insulin the prevention of gluconeogenesis The partial defense of the body against this is as follows When the level of blood glucose falls to 60 mgs, adrenalin stimulates the pituitary to the further production of ACTH and cortisone promoting gluconeogenesis By a complex mechanism exercise appears to enhance the hypoglycemic effect of insulin It tends to increase the volume of distribution of certain sugars and probably accelerates the hexokinase system Inherent conditions preventing the absorption of sugar, or preventing the formation of glycogen or gluconeogenesis as well as sudden removal of diabetogenic substances will precipitate hypoglycemia in the diabetic receiving insulin therapy

(b) Disturbed Chemistry

In addition to low levels of blood glucose, 60 mg or below, other changes in chemistry are observed The non protein nitrogen and calcium of the blood are low Potassium, phosphorus and sodium may be elevated In severe prolonged hypoglycemia, potassium levels fall sodium and chloride levels may rise to abnormally high degrees The electrocardiogram shows T waves to be low or flat, QRS to be broad Extrasystoles, auricular fibrillation and prolongation of the PR interval occur The electroencephalogram shows preponderance of slow waves The spinal fluid shows increased pressure and diminished sugar content The white blood count may be moderately elevated with a relative lymphocytosis and depression of eosinophiles The respiratory quotient may be low

(c) Pathology

Hypoglycemic encephalopathy is a recognized pathological entity Diffuse cortical destruction is reported, as well as degeneration in glia cells, ganglion cells, edema, extravasation of blood and actual hemorrhages

(d) Etiology

The clinical cause of insulin hypoglycemia is an actual or relative overdose of insulin Thus the usual and unusual clinical causes include (1) an overdose of insulin to anticipate extra food, (2) a mistake in the measurement of insulin (3) delayed time of a meal or a snack, (4) inadequate food intake, (5) unusual exercise, (6) change in the site of injection of insulin These are the common errors made by the patient Those for which the physician is responsible are *(1) overestimation of the needs* of the new patient, (2) failure to anticipate improvement, as in the expected remission in children, or following the correction of such diabetogenic states as hyperthyroidism, ketosis or

infection, and (3) such superimposed states as gastro-intestinal upsets, hepatitis, early pregnancy, anxiety, Addison's disease, Simond's disease, tuberculosis and diabetic nephropathy

(e) *Symptoms*

The symptoms of insulin hypoglycemia are those of disturbed function of the entire nervous system The earliest ones are due to stimulation of the sympathetic nervous system and are cardiac and muscular in type They include increased activity of the sweat glands, gastric glands and are associated with parasthesias Thus, the blood pressure falls, the pulse is slow, tremors are present There will be muscle weakness, sweating and excessive hunger With the administration of simple forms of treatment, the insulin reaction is usually controlled at this level If the condition progresses, the central nervous system becomes involved The symptoms may be cortico spinal, including hallucinations, apraxia, amnesia, aphasia, clonic and tonic cramps, convulsions of the Jacksonian type, positive Babinski, loss of reflexes, incontinence, double vision and mono- and paraplegias Striothalmic lesions are observed in which the behavior becomes akinetic or hyperkinetic There may be choriform motion, grimacing, loud speaking compulsive crying and laughing The bulbopontine lesions include slow pupillary reaction, mask like expression and difficult speech The central vegetative symptoms include fluctuations of temperature, fall to low levels and subsequently a rise to high temperatures, somnolence, faintness, collapse and temporary blindness Psychical manifestations also occur They may be stupor, catatonia, dementia, psychoses, hysteria, anxiety and depression

(f) *Signs*

The signs of hypoglycemia are most commonly pallor, occasionally flushed skin, sweating although the skin may

also be dry, rise of blood pressure, the full bounding pulse and the positive neurological findings The danger signals of parasympathetic involvement include coma, shallow respiration, tremendous slowing of the heart, pale skin contracted pupils without reaction, sweating, sub normal temperature, loss of corneal reflex and loss of other reflexes

The diagnosis of *hypoglycemia is made upon the level of* blood glucose, namely 60 mg or below Although the majority of these severe cases will respond to the administration of glucose intravenously, hypoglycemia cannot be ruled out if the patient fails to make a rapid and satisfactory immediate response The urine is often misleading, especially if it is the first voided specimen

(g) *Preventive Treatment*

Prevention of hypoglycemia is sought in two ways, by anticipatory meals and careful regulation of the daily dose of insulin Since the maximum fall of blood sugar when regular insulin is used is some three hours after administration, a snack consisting of 10 to 15 grams of carbohydrate is prescribed within the third hour following the injection of this insulin With Globin, NPH, Lente and the common 2 1 mixtures of protamine and regular insulin the maximum fall of blood sugar is some eight hours after administration so that such patients require a snack approximately seven hours after the administration of insulin, again usually in the form of 10 to 15 grams of carbohydrate Thus, if insulin is given at 8 o'clock in the morning, users of regular insulin should receive 10-15 grams of carbohydrate at 11 o'clock Users of the intermediate acting insulins should receive a snack containing 10-15 grams of carbohydrate at 3 30 o'clock. When protamine zinc insulin is used, in the unmixed form, the fall of blood sugar is some 12 to 24 hours after administration, so an adequate bedtime snack of 15 grams of carbohydrate is recommended When the second

of two voided specimens can be obtained, the pre-breakfast test becomes the guide for the morning dose of protamine zinc, globin, NPH or Lente insulins The pre lunch test becomes the guide for changing the dose of regular insulin used in combination with the intermediate acting insulin If a bedtime dose of intermediate acting insulin is necessary, then the pre breakfast test becomes the guide for increasing or decreasing the bedtime dose The pre lunch test remains the guide for the changes in rapidly acting insulin and the pre supper test becomes the guide for changing the dose of the morning intermediate acting insulin In like manner, regular insulin should be reduced if a reaction occurs in the morning between breakfast and lunch If a reaction occurs in the late afternoon the intermediate acting insulin should be reduced by 4-8 units or if the reaction occurs during the night the long acting insulin should be reduced Similarly, anticipation of glycosuria rather than its correction when long acting insulins are used prevents much unnecessary hypoglycemia

(h) *Use of Anticonvulsant Drugs*

Anticonvulsant drugs are recommended for patients who show electroencephalographic changes consistent with petit mal, grand mal or psychomotor behavior and also for those patients who show slowing of the waves under such physiological stress as over breathing. These may be phenobarbital, dilantin, diamox, mesantoin tridione or meberal

(i) *Treatment*

The treatment of hypoglycemia consists of the oral administration of carbohydrate-containing substances if the patient is conscious Orange juice, Coca Cola or actual sugar may be employed The earlier the carbohydrate is taken, the smaller will be the amount necessary to control the symptoms If the patient is unconscious, a member of the

family may administer a small quantity of adrenalin chloride 1 1000 solution, $\frac{1}{10}$ of a cc for a small child, up to $\frac{3}{10}$ of a cc for an adult and this may be repeated in 15 minutes. There is also some evidence that the administration of glucose by rectum in the presence of hypoglycemia is effective The physician's first choice, however, is the administration of glucose intravenously in the form of a 50 per cent solution Twenty cc of a 50 per cent solution of glucose is usually adequate, but more glucose may be required

(j) *Treatment of Patient with Prolonged Unconsciousness*

If the patient has been unconscious for many hours, or if convulsions have been present, then the following program is recommended intravenous glucose in the form of a constant vena-clysis, for a child or small adult, 150 grams of glucose during 24 hours, for an average sized adult, 300 grams in 24 hours To this solution 2½ to 5 cc of adrenalin chloride may be added Anticonvulsant drugs may be administered in the form of sodium luminal intramuscularly or dilantin by stomach tube A transfusion of fresh whole blood, cortisone, suction, airway, and oxygen may be used as indicated The electrolyte pattern should be followed carefully because with central nervous system damage, the potassium may fall and the sodium and chloride rise to tremendously high levels A solution of 20 per cent dextrose containing 2 grams of hydrogen potassium phosphate and .2 gram of dihydrogen potassium phosphate per liter has also been recommended to prevent this possible disturbance in electrolyte pattern

(k) *Identification*

All diabetic patients taking insulin should have identification in the form of cards, bracelets or lockets giving not only names and addresses, but also the diagnosis of diabetes

(l) *Prognosis, Immediate and Remote*

The prognosis is always good, if treatment is prompt Among patients with prolonged unconsciousness, it is the custom of the authors to withhold a poor prognosis for complete recovery until a period of 6 weeks has elapsed. *When fatalities occur following hypoglycemia, the most* common clinical error has been the administration of insulin, even a relatively small dose, during the episodes of hypoglycemic unconsciousness Insulin is sometimes administered by the family and sometimes by the attending physician Possible remote complications of hypoglycemia include lesions of the nervous system, heart, retina and kidney

(m) *Differential Diagnosis*

Hypoglycemia must be differentiated from ketoacidosis, epilepsy, alcoholism, and cerebrovascular accidents Electroencephalograms, levels for blood sugar and samples of blood or expired air tested for alcohol will differentiate the first three, time will usually give satisfactory evidence of the last.

CHAPTER VI

INSULIN RESISTANCE

The term "insulin resistance" has been used in reports of many individuals in whom excessively large amounts of insulin have been required for treatment of diabetes or other purposes. The existence of diabetes is not a prerequisite for resistance since it is well known that in the insulin treatment of schizophrenia certain patients require increasingly large doses of insulin to produce the hypoglycemic coma desired. A definition of insulin resistance in terms of insulin dosage is not easy. If it is remembered that in human beings in whom the pancreas is removed the amount of insulin required usually is only 40-60 units a day, then it might be considered that any daily dosage of insulin required by diabetic patients in excess of this amount represented some degree of resistance. However, in recent years, it has become somewhat customary to use the term "insulin resistance" chiefly for diabetic patients who without ketosis or after periods of infection, require over 200 units of insulin daily when on a standard diabetic diet and at normal activity.

A large group of patients have required huge amounts of insulin for recovery from emergency conditions such as diabetic acidosis and coma, or during such conditions as myocardial infarction. Such patients have usually returned to their usual levels of insulin dosage following recovery from such processes. Cases of diabetic coma requiring from 1000 to 5000 units of insulin during a period of 24 hours have not been too rare. Massive doses of 20,000 to 60,000 units in 24 hour periods have been used under exceptional circum

stances in patients with diabetic acidosis or myocardial infarction In such patients the presence of such complicating conditions has not been recognized during their life but found only at autopsy

Among 20 insulin resistant patients seen at the New England Deaconess Hospital the ages varied from 12 years to 73 years, only 2 cases were under 20 years of age, so that insulin resistance is comparatively rare in young patients The duration of diabetes may vary from a period of days to as much as 21 years In many of the patients with insulin resistance, no complicating condition can be found to explain the resistance

Factors responsible for insulin resistance have been classified as follows

1 Alterations in the functional integrity and innate characteristics of the tissues which contribute sugar to and remove sugar from the blood as in cases of hemochromatosis and other liver diseases

2 Alterations in the cellular enzyme systems which catalyze the chain of reactions involved in the formation and disappearance of glucose

3 Variations in activity of the regulators of tissue functions, the endocrine system and the central nervous system Under this heading were included patients in whom an excess of contra insulin hormones occurred as is found in patients with pituitary hyperfunction, acromegaly, Cushing's syndrome, mid brain cyst, hyperthyroidism and pheochromocytoma Also would be included under this classification patients who might be considered to have an insufficiency of the insulin because of delayed absorption, immunologic inactivation or neutralization or infections with possible insulin inhibition or destruction

Insulin resistance has in some cases been related to the development of antibodies and the degree of resistance parallels their concentration Although insulin is a poor antigen, in some patients, particularly where infect

present, the antibody mechanism is altered In one of our patients with insulin resistance, the patient, an elderly Jewish woman, had formerly required only 10 units of insulin Without any complication whatsoever insulin resistance developed At the time of observation she was taking 1500 units a day There were marked insulin atrophies not only at the sites where her insulin had been injected but also in the breasts where no previous injection of insulin had been made The insulin requirement had risen steadily It was found that when a moderate dose of insulin was given by vein it had a much more marked effect upon the respiratory quotient than a dose several times that high given under the skin The suspicion was raised that there might be some change in the process of absorption of insulin A special radio-active insulin compound with iodine was prepared and administered to this patient together with a group of patients acting as controls Using a Geiger Counter, it was found that the rate at which insulin left the site of injection was very slow in comparison with the rate observed in normal individuals and in diabetic patients without resistance In her case, as in patients with fat hypertrophy insulin administration, the slow rate of absorption of insulin seemed to be one factor although not perhaps the only factor in her insulin resistance The use of human insulin did not alter this patient's insulin requirement The same number of units was required to bring about a change in blood sugar with human insulin as with insulin derived from animal pancreas

In treatment it is generally agreed that it is of vital importance to find that insulin dose, no matter what its size, which is necessary for the individual and to furnish it for as long as necessary If this is done, barring complications, there is reasonable hope that insulin resistance will gradually disappear The use of a preparation of insulin with high concentration up to 500 units per cc was begun some years ago At present such preparations are available through

hospital dispensaries One fact which should not be forgotten is that the use of such high-concentration insulin even in unmodified forms is accompanied by marked prolongation of the duration of insulin action Thus, in some patients it is possible to give a single dose of regular insulin once daily before breakfast and have the effect last throughout 24 or more hours

Recently, cases have been described, in which the progressive development of insulin resistance has been accompanied by increase in the serum concentration of globulin The use of ACTH then was followed by a rapid reduction in insulin requirement

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CHAPTER VII

ORAL TREATMENT OF DIABETES WITH SULFONAMIDES

The fact that sulfonamide derivatives lower the blood sugar levels has been frequently noted since 1941 The earlier compounds apparently were found too toxic for continued clinical use During 1955 reports appeared that two among the many sulfonamide derivatives under investigation had been used to reduce the blood sugar levels in diabetic patients Information is available chiefly on carbutamide (BZ-55) and the compound tolbutamide (Orinase)

These compounds, given orally or parenterally, produce a drop in blood sugar levels The one feature which seems necessary to bring about this effect is the presence of a sufficient number of islands of Langerhans to produce a certain amount of insulin or else insulin given exogenously

Mode of Action The effects of the drug seem to be multiple, but the major effect is apparently due to a stimulation of the islands of Langerhans to release or produce insulin In animals degranulation of the islets may be produced within a few hours and after a prolonged period of injections it has been reported that the size of the islands has been measurably increased in animals The question arises whether such long-continued stimulation of the islands of Langerhans will be in a period of years beneficial

Other effects include the possibility that the rate of destruction of insulin in the organism is diminished

Results Our own experience coincides with the results of others in that the drug is useful chiefly in elderly patients with diabetes of short duration or who have had insulin for

a relatively short period of time and who do not belong in the insulin sensitive or "brittle" class of diabetics The drug has been very ineffective in juvenile diabetics and patients with acidosis or other serious complications It has been possible in this selected group often to replace 10 to 50 units of insulin a day with tablets of BZ-55 or of Orinase BZ-55 (carbutamide) seems more effective gram for gram

Methods At present patients are selected by means of a four hour test Insulin must be omitted for 48 hours and the patient tested in the fasting state Then a fasting blood sugar is determined 3 grams of the drug given by mouth and the blood sugar level determined four hours later Patients who show a drop in blood sugar level of from 20 to 40 per cent or more in that period of time are usually sensitive to the drug and will do well upon treatment Usually patients have been started with 2 grams of carbutamide or tolbutamide per day and the dose gradually reduced to as little as 1 gram per day

In our group of approximately 200 patients a third have received the drug for periods exceeding four months Those occasional patients elderly who have been apparently insulin resistant have been able to decrease the insulin dose from 200 units to a much smaller dose or even to give it up Toxic effects upon the skin consisting of rashes have been rare Since insulin is a specific hormone essential in diabetes its indiscriminate substitution by sulfonamides in cases of acidosis insulin sensitive cases and youthful patients or patients with surgical complications might be disastrous

Hypoglycemia may occur with symptoms comparable to those seen in the hypoglycemic reactions following the use of long acting insulin It must be remembered that traces of these drugs may be found in the blood for periods up to 72 hours or even more after ingestion

Only time will tell whether these drugs will aid in correcting the fundamental disorder of diabetes in appropriately selected cases as well as does insulin

CHAPTER VIII

DIABETIC ACIDOSIS AND COMA

Introduction

Diabetic coma is the unique complication of diabetes resulting from insulin deficiency and failure of diabetic control. It does not occur while diabetes is under good control although the development of certain complications may rapidly take the diabetes out of control. Although the word "coma" implies a state of unconsciousness, the patient who is developing diabetic ketosis may be in serious danger long before he is unconscious and, therefore, the word diabetic coma may well be used for early as well as the late stages. Deaths from coma have been greatly reduced but may still occur because of ignorance, delay in diagnosis or actual neglect. In recent years hypokalemia* has been recognized as a lethal complication occurring during ketosis and in the course of treatment. Fortunately, it is readily detected and appropriate treatment may be given. Diabetic coma due to ketosis is (1) always an emergency, (2) always remediable if treated early and adequately, and (3) preventable.

Nature of Diabetic Acidosis and Coma

Diabetic ketosis results from an intoxication caused by the accumulation of excess products of intermediary protein and fat metabolism dependent upon insulin deficiency. Drowsiness and coma represent the reaction of the brain to the ketosis, dehydration, acidosis and mineral depletion.

Common etiologic factors are (1) insufficient insulin or

* Potassium is present in normal serum in concentrations of 3.8-4.3 m Eq per liter (14.8-16.8 mg per 100 cc.)

omission of insulin, (2) infectious complications, (3) resistance to insulin action, (4) anesthesia, shock, (5) vomiting and diarrhea from any cause, (6) thyrotoxicosis, (7) pregnancy and toxemias of pregnancy In our experience, dietary errors are the most frequent among the etiologic factors in the development of ketosis Gross dietary excess with increased hyperglycemia and glycosuria, like the omission of insulin, leads to ketosis

With insufficient insulin dosage, especially in the presence of infection, a rapid rise in the blood sugar level and glycosuria occur Loss of calories due to the faulty carbohydrate utilization stimulates the mobilization and utilization of protein and fat The depot fat is mobilized, fatty acids are transported to the liver where conversion to ketone bodies takes place Since it is not possible for fatty acids and ketone bodies to replace completely the caloric deficiency imposed by impaired carbohydrate utilization, the tissue needs are never satisfied and the stimulation for increased fat and protein utilization is continued in spite of the overabundant supply of this source of energy As the metabolites of protein and fat combustion are formed in excess of the capacity to use them, the blood level increases and finally exceeds the renal threshold The serum bicarbonate level falls as base combines with the acid metabolites and large quantities of fixed base, particularly sodium and potassium, are lost in the urine with the acid end products The loss of this fixed base results in acidosis and dehydration

Acetone is the first of the ketone bodies to be found in the urine following its formation from aceto-acetic acid As the ketosis increases, diacetic acid itself and finally beta-hydroxybutyric acid appear With impairment of renal function large quantities of the acid metabolites may accumulate in the serum, even though no large quantities of these substances are found in the urine In early stages the amount of total ketone bodies in the blood plasma may be only 25 to 50 mg per 100 cc, but in patients who have reached

stage of unconsciousness, usually the values will be from 100 to 200 mg per 100 cc A rough qualitative test for acetone in the serum, described on page 337 gives bedside aid in interpreting the degree of ketonemia

Signs and Symptoms

The early symptoms of ketosis may be indefinite, deluding patient and physician The patient may not appear gravely ill The complaints of constipation, abdominal pain or head ache, nausea or loss of weight may not suggest to the patient the early development of diabetic ketosis unless he has this early stage clearly in mind However, the urine will show a positive test for sugar and ketone bodies and blood sugar tests will be confirmative

The patient nearing unconsciousness or actually in coma appears desperately ill A rapid pulse and a falling blood pressure, together with marked dryness of the skin and mucous membranes are evident The cheeks may be flushed air hunger is shown by the increased rate and the depth of respiration Kussmaul breathing is most striking because of the force and depth of the respiratory movements and the extreme weakness and indeed flaccidity of the patient Occasionally patients in diabetic coma are active and thrashing about in bed, but exhaustion is more frequent The replacement of the deep respiration of air hunger by feeble, rapid and gasping respiration is an indication of the stage of exhaustion and always ominous The sweetish odor of acetone on the breath may easily be recognized by some, but not so easily recognized by others The general dryness of the skin, the axillae, the groin, the palms, the tongue and the soft eyeballs are of importance as a characteristic of the dehydration of diabetic ketosis in contrast to the moist, sweating of the skin in conditions such as insulin hypoglycemia or shock from other conditions

Heart sounds may be feeble and distant, respiratory mur

mur may be slightly amphoric and this quality may be recognized even before the depth of respiration is obvious Extremities are cold and the body temperature is usually subnormal In patients who have had such an infection as pneumonia, the development of severe ketosis may reduce the temperature to subnormal and yet within a few hours after the control of the acidosis, the fever will return The presence of fever in a ketotic patient indicates some infection The tenderness and rigidity sometimes seen in the abdomen together with marked leukocytosis and vomiting may lead to diagnostic difficulty This finding in some patients has been so extreme that operation has been performed with a pre-operative diagnosis of perforated viscus, spreading peritonitis or pancreatitis When actual doubt exists it may be safer in diabetic ketosis to perform an unnecessary operation than to run the risk of missing an acute appendicitis

Reflexes tend to be sluggish or absent Sometimes the reflexes have been present on admission, but with the development of hypokalemia their disappearance may be an important clue to the diagnosis Frequently the lack of an adequate history in the case of an unconscious patient or a patient who has not been under the observation of friends of the family make it easy to overlook pneumonia Otitis media and other infections such as furuncles, carbuncles, pyelonephritis, gangrene or septicemia are among the complications which may easily precipitate ketosis

Differential Diagnosis

Conditions which may be confused with diabetic coma, especially in the patient who is known to have diabetes are an intracranial hemorrhage, uremia and severe insulin reactions Trauma to the head, drug poisoning, meningitis or brain tumor deserve special consideration since glycosuria is frequently a result of these conditions

a.) *Hypoglycemia*

Perhaps one of the most fatal errors in internal medicine is that of giving insulin to a patient who already has hypoglycemia Patients in hypoglycemia are not always sweating or moist Their mental behavior may be of many patterns

TABLE 18

DIFFERENTIAL DIAGNOSIS IN HYPOGLYCEMIA AND DIABETIC COMA

	Hypoglycemia	*Diabetic Coma*
History	Insufficient food, excess insulin, excess exercise	Insufficient insulin infection gastrointestinal upset
Onset	Following short-acting insulin Suddenly, a few hours after injection Following long acting insulin Relatively slower, many hours after injection	Slow hours or days
Course	Anxiety, sweating, hunger, headache, diplopia incoordination, twitching convulsions, coma (Headache nausea and haziness especially following long acting insulin)	Polyuria polydipsia anorexia, nausea, vomiting labored deep breathing weakness drowsiness possibly fever and abdominal pain, coma
Physical findings	[illegible]	[illegible]
Laboratory findings	Second urine specimen sugar and ketone-free low blood sugar, normal serum CO_2	Urine contains sugar and ketone bodies, high blood sugar, low serum CO_2

A urine specimen obtained by catheter should be sugar free but the urine thus obtained may show sugar because it has been long in the bladder A blood sugar test is essential for distinguishing hypoglycemia from diabetic ketosis The most important points in distinguishing between unconsciousness

due to hypoglycemia and to ketosis are present in Table 18 When in doubt, a small amount of glucose, injected intravenously, 5-10 grams, often brings about rapid clinical improvement in patients with hypoglycemia If the hypoglycemia is due to protamine zinc insulin, the patient may again develop hypoglycemia 20-30 minutes later and require further treatment

b) *Intracranial Hemorrhage in Diabetes*

Here the onset of unconsciousness has been relatively sudden, although sometimes a history of severe headache during the days preceding unconsciousness may be a little confusing Differences in reflexes, muscle tone and in muscle contour may be helpful Again, the patient unconscious as a result of hemorrhage is not so markedly dehydrated The skin is usually moist and the intraocular tension is not decreased The blood pressure is variably elevated The spinal fluid may contain gross blood The degree of unconsciousness is very marked in contrast to the only moderate elevation of the blood sugar when compared with the findings in diabetic coma Little or no acetonuria or acetonemia is present and the carbon dioxide-combining power of the blood is not greatly depressed

c) *Uremia in Diabetes*

The problem of differentiating uremia is becoming more frequent today as more diabetic patients are to be found, who because of uncontrolled diabetes for many years have reached the stage of diabetic nephropathy When nitrogen retention and uremia develop in such patients nausea, vomiting ketonuria and ketonemia may occur The elevation of the blood sugar may exceed 500 mg per cent Depression of the CO_2 content of the blood may be such as to reach the level usually seen in diabetic ketosis Indeed, one may be dealing with a situation in which both diabetic uremia and diabetic coma are present This will require

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Course	Anxiety sweating hunger head ache diplopia incoordination twitching convulsions coma (Headache nausea and haziness especially following long acting insulin)	Polyuria polydipsia anorexia nausea vomiting labored deep breathing weakness drowsiness possibly fever and abdominal pain coma
Physical findings	Pale moist skin full rapid pulse dilated pupils normal breath	Florid dry skin Kussmaul breathing with acetone odor weak
Laboratory findings	Second urine specimen sugar and ketone-free low blood sugar normal serum CO_2	Urine contains sugar and ketone bodies high blood sugar low serum CO_2

A urine specimen obtained by catheter should be sugar free but the urine thus obtained may show sugar because it has been long in the bladder A blood sugar test is *essential for* distinguishing hypoglycemia from diabetic ketosis The most important points in distinguishing between unconsciousness

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careful estimation of the relative importance of the two factors Diabetic coma is usually accompanied by an increase in insulin resistance and will require rather large doses of insulin On the other hand uremia in diabetics, while it may require moderately increased insulin is not accompanied usually by marked insulin resistance It will be possible to make grave errors in giving too large doses of insulin to such a patient In the non diabetic patient with uremia, no such difficulties will occur In the diabetic patient who has uremia only, but no real ketosis as revealed by the blood level for acetone, increased blood pressure, cardiac enlargement, a typical uremic odor of the breath, and the absence of acetone in blood and urine will be helpful

d) *Meningitis*

Meningitis will be recognized through reflex changes a stiff neck, the Kernig s sign, fever and the increased leukocytosis in the cerebrospinal fluid

e) *Brain Tumor*

Brain tumor may also cause nausea and vomiting of the projectile type during some days before final unconsciousness However, the lack of air hunger, the slow pulse and usually changes in the eye grounds will lead to the direct diagnosis

Prognosis

Death in the young diabetic patient has become rare provided the diagnosis is made before the patient is anuric and provided the patient does not have complications in themselves insuperable Prognosis is grave if an adult patient has been completely unconscious for more than twelve hours, if he is over 45 years of age and the systolic blood pressure is below 50 mm of mercury, if severe complicating infections, or a perforated viscus, or peritonitis, or renal fail

ure with anuria is present, or if coronary infarction is present High levels of sugar in the blood above 1000 mg per 100 cc and a CO_2 concentration of the blood below 6 mEq are usually found in patients who have some severe complication The mortality increases in the aged The degree and duration of unconsciousness are important Thus, in our patients at the Deaconess Hospital the mortality of patients profoundly unconscious was 35 per cent in the years prior to 1940 Since 1940, with more aggressive use of insulin and particularly with earlier use of insulin through the cooperation of family doctors who have given insulin at home before the patient's arrival at the hospital, the mortality in unconscious patients has fallen to 12 per cent

Renal function is often a determining factor in the prognosis It is common to have nitrogen retention with a non protein nitrogen value of 50 70 mg per 100 cc at the height of diabetic ketosis However, values exceeding 100 mg are distinctly more serious and particularly if due to serious complicating renal disease such as chronic pyelonephritis or chronic nephritis In patients with complete anuria lasting more than 24 hours, the mortality rate may be expected to exceed 50 per cent

Treatment (see p 276 for acidosis in childhood)

In Table 19 is summarized an outline of treatment which we have found useful It is still true that in many instances the amount of insulin given is too small in the early hours of acidosis A patient developing or actually in diabetic coma needs insulin immediately When information making certain the diagnosis of diabetic acidosis is received over the telephone, insulin in dosage varying from 20 to 50 or even 100 units can usually be given safely Any patient in serious acidosis deserves treatment in a hospital As soon as plans for the patient s admission are known, preparation for his arrival and treatment should be made

Hot water bottles, blankets, stomach and rectal tubes, salt and glucose solutions, insulin and stimulants should be assembled A special coma cart with these materials has proved of great use in many hospitals

TABLE 19

Treatment of Diabetic Acidosis and Coma

Diabetic acidosis is the result of insulin deficiency Nausea vomiting abdominal pain dehydration shock, air hunger, drowsiness lead to coma and (if insufficiently treated) death Important chemical features are *hyperglycemia, glycosuria, ketonemia, ketonuria reduction* of plasma CO_2, depletion of electrolytes, especially potassium

FIRST HOUR AFTER ADMISSION Special nurse, preferably experienced in coma treatment, for the first few hours

LABORATORY

1 *Urine* Examine for *sugar, acetone diacetic acid albumin,* coma casts and pyuria Catheterize if necessary
2 *Blood* Test for sugar, CO_2 content and non protein nitrogen, with emergency report within an hour White blood count. Serum potassium if indicated Hematocrit

CLINICAL

3 *Search for complications and establish diagnosis*
   A History to explain cause of coma
   B Physical examination, noting particularly—
      (a) State of consciousness, type of respiration pulse rate, blood pressure, and rectal temperature
      (b) Look for soft eyeballs, dry tongue, dilated stomach, cold and mottled skin, impacted rectum, and tendon *reflexes*
   C X ray chest and abdomen when possible
   D ECG (a) coronary (b) potassium changes
4 *Insulin* 50 to 100 units of regular insulin subcutaneously at once for adults In severe cases especially with circulatory collapse, give insulin intravenously If blood sugar exceeds 800 mg per 100 c c and if the blood CO_2 content is 9 millimols per liter (20 volumes per cent) or less, the dose will need to be repeated The insulin dose would be proportionately less (20 to 40 units) in young children, especially if ... between ...th blood

5 *Gastric Lavage* Aspirate completely and wash stomach with warm water with greatest care
6 Normal saline intravenously, 2000 c c It is desirable to change to a solution of saline lactate after the first liter of saline solution is given (to 700 c c saline add 1 ampoule (40 c c) 1 molar lactate and make up to 1000 c c with sterile distilled water) *If lactate is unavailable, normal salt solution* may be continued Avoid too rapid administration, especially in older patients
7 Keep patient warm yet avoid burns, as from hot water bottle

SECOND TO SIXTH HOUR The gravity of the case may require repetition of first hour s total insulin in the second hour

8 Give potassium solutions by vein for definite indications (a) *when blood analysis or ECG clearly indicates hypokalemia*, (b) when potassium depletion is probably present as result of prolonged serious ketosis and/or deficient potassium intake, c) only in the presence of adequate urinary output, 25 mEq K per hour up to 100 mEq may be given
9 Repeat blood sugar and CO_2 determinations after three or four hours For rising blood sugar give insulin hourly 50 200 units or more, according to estimate of prognosis
10 Fluids by mouth (as soon as tolerated), limited to 100 120 c c per hour of broth, ginger ale, orange juice tea or coffee, *to be sipped by* patient or spooned by nurse *For children* limit to 50 c c per hour at first Then, if nausea and vomiting recur, withhold fluids orally for 2 to 6 hours (lavage stomach again if indicated) and then resume
11 *Enema* for cleansing and to relieve abdominal distension
12 Record and note changes in blood pressure pulse and temperature hourly *Consider transfusion or vasopressor* drugs if in deep shock
13 Urinalysis for sugar and diacetic acid every hour Record hourly output as index of dehydration and renal function
14 *Antibiotics* (parenteral) as penicillin, streptomycin or aureomycin frequently needed
15 *Urinary output* Record hourly and note with alarm any sign of oliguria 1500 c c intravenous saline lactate for persisting shock Repeat as necessary For anuria associated with hypochloremia give 50 c c of 10 per cent salt solution intravenously Beware producing excessive diuresis with consequent loss of base especially of potassium (by too rapid administration of I V Fluid) For anuria, associated with hyperchloremia, omit all saline using only glucose in *intravenously Volume of such fluids may need limit* 1000 c c in 24 hours

SIXTH TO TWENTY FOURTH HOUR

16 Repeat blood sugar and CO_2 determinations Give insulin 50 200 units if blood sugar and CO_2 levels are not improving Insulin (regular) may be given according to urine tests every 1 to 4 hours if fall in blood sugar has been satisfactory

If test is—	Red	Orange	Yellow	Green	Blue	
Give—	20	16	12	0	0	units

For young children give half dose

17 Soft or liquid food such as oatmeal gruel orange juice or milk diluted half and half with lime water not to exceed 10 gm carbohydrate per hour Glucose (5% in saline) I V at rate of 200 c c per hour only when blood sugar approaches normal

18 [illegible]

are present

SECOND DAY AND SUCCEEDING DAYS

19 Soft Food—Diet carbohydrate 100 to 150 gms protein 50 gms fat 50 gms Gradually return to standard diabetic diet for age and weight with carbohydrate 150 to 200 gms protein *60 to 100 gms fat 60 to 120 gms daily*

ADDITIONAL NOTES

I Differential diagnosis should include the acidosis of diabetic nephropathy occurring in patients with diabetes of *long duration* Uremia may result in retention of ketone bodies in the blood plasma although they may be absent or reduced in concentration in the urine Examine plasma for acetone by nitroprusside test * or quantitate ketone bodies in blood

Total Ketones in Blood

	Mg per 100 c c
Normal	0 to 5
Non Diabetic Uremia	5 to 60
Diabetic Coma	50 to 200+

* *Plasma Acetone Test*
4 c c of blood in an oxalate tube centrifuged until clear plasma obtained Make solutions of 1 in 2 1 in 4 and 1 in 8 with normal *saline or tap water* Place 3 drops of undiluted plasma and the three dilutions on separate small mounds of acetone test powder At the end of 60 seconds read the color (do not allow to stand longer) Depth of purple color indicates concentration of acetone and in some cases may be used as a *clue to insulin resistance*

II To avoid pulmonary edema rarely exceed 5000 c c parenteral fluid in 24 hours and check frequently for signs of edema If urinary output exceeds 40 c c per hour after parenteral fluid has been given up to 3000 c c grave dehydration no longer exists

III Electrolyte containing solutions Potassium should not be given intravenously in excess of 25 mEq per hour!! Rarely is it wise to exceed 100 mEq in 12 hours unless definite hypopotassemia is present and urine secretion is ample After 12 to 24 hours if 3 to 4 grams potassium cannot be taken by the patient in diabetic diet a simple solution may be taken in divided amounts Thus two hundred c c orange juice plus 2 grams potassium phosphate may be diluted with water to 500 c c Of this give 100 c c per hour With fall in blood sugar and need for potassium a 5 c c ampoule (2 grams dibasic potassium phosphate and 0 4 gram monobasic potassium phosphate) may be added to 1000 c c of 5 per cent glucose for intravenous administration if indicated

IV Electrocardiographic signs of

A Low serum potassium (below 3 0 mEq)
   1 Lowered or inverted T waves
   2 Depressed ST segments
   3 Lengthened QT, or appearance of U wave
   4 Prolonged P R interval

B High serum potassium (above 6 0 mEq)
   1 High peaked T waves
   2 Wide QRS
   3 Disappearance of P waves
   4 AV dissociation
   5 Final disorganization of ECG

Note A normal ECG does not exclude K deficiency The above changes may not always be due to hypokalemia

Insulin

In Table 20 is summarized the insulin dosage (regular and not protamine insulin) in the first three and the first twenty four hours, respectively, of 213 cases of coma treated at the Deaconess Hospital between 1946 and 1953 The proper goal is to ascertain as nearly as possible the patient's total insulin requirement and to administer this dose as soon after the diagnosis as possible Often one cannot predict the insulin requirement until the second blood sugar test is available to demonstrate the degree of effectiveness of the first dose In many patients, the initial dose of insulin

TABLE 20

COMA 213 CASES 1946-1953

Blood Sugar on Admission Mg	*Cases (No)*	*Avg Insulin 1st 3 Hours (Units)*	*Avg Insulin 1st 24 Hours (Units)*
1 300-1 600	3	883	1 683
1 000-1 300	13	514	825
600-1 000	65	335	526
400- 600	69	209	329
200- 400	60	99	151
100- 200*	3	71	140

* Low values due to insulin given en route to hospital

may be only 40 or 50 units particularly in children or young patients with diabetes of short duration For adults larger doses are needed In severe cases, especially those with circulatory collapse half the insulin dose is usually given intravenously It will be seen from Table 20 that the insulin given in the first three hours after admission to the hospital has actually been about 50 or 60 per cent of the total amount required in the first 24 hours Our feeling at present is that unless at least 50 per cent of the total amount required to re establish normal metabolism is given in the first three hours the speed of insulin administration has been too slow The urgency of giving large doses of insulin in the first three hours rests upon the necessity of controlling polyuria glycosuria and hyperglycemia The excessive hyperosmolarity of the blood due to the excessive concentration of glucose exerts tremendous osmotic force, causing withdrawal of water from cells and consequent intracellular dehydration The more rapidly the concentration of glucose can be reduced, the more rapidly will intracellular rehydration proceed Our custom usually is to give insulin in divided doses at frequent intervals sometimes as often as *once in fifteen* to thirty minutes In the more severely ill patients with circulatory collapse insulin is commonly given intravenously occasionally into the jugular vein

Fluid Therapy

The objects of fluid therapy, then, are (1) to correct the hyperchloremia and hyperosmolarity of the patient's extra cellular fluid, (2) to provide sodium, chloride and water to expand the extracellular fluid volume, (3) to correct intra cellular dehydration, and, finally, (4) to provide potassium and phosphate necessary for the restoration of stores of intracellular glycogen and protein The extent of the deficit in water and chloride would depend upon the duration and severity of the uncontrolled diabetes In patients without previous diagnosis and treatment of diabetes the condition may be extreme Loss of water may amount to 10 or 15 per cent of the body weight A total of 4 to 7 liters of fluid is frequently required in the first 24 hours of treatment Most patients will recover with the use of ordinary physiological saline solution alone However, in patients with severe depletion the ideal replacement fluid contains sodium in excess of chloride, and water in excess of sodium—that is, a slightly hypotonic solution of a mixture of sodium chloride and sodium lactate as indicated in the second to the sixth hour of the Outline of Treatment

If the pH, electrolyte, and water content of the extracellular fluid are restored, and the patient receives adequate fluid, intracellular dehydration will soon be corrected The restoration of adequate potassium and phosphate is best accomplished by the diet, since the intravenous administration of potassium in patients with poor renal function may lead to hyperpotassemia In an occasional patient, the rapid expansion of the extracellular fluid with sodium chloride may result in precipitous drop in serum potassium and the development of clinical and electrocardiographic abnormalities The development of weakness or paralysis in a patient otherwise responding well to therapy demands a rapid determination of serum K or an electrocardiogram, where flattening of the T waves and a prolonged Q-T interval are

indicative of hypopotassemia In these patients 40 to 50 mEq of potassium acetate may be added to a liter of saline, and the liter infused over a period of three to four hours This may be repeated in twenty four hours if necessary

The measurement of dehydration is difficult It is important to give enough fluid and yet to avoid excessive amounts In general, one can say that a patient who is excreting 40 cc of urine per hour after parenteral fluid is no longer seriously dehydrated

Hypertonic solutions should never be given to these patients A 10 per cent solution of dextrose contains 556 milliosmols per liter, as compared to a normal body water osmolarity of 320, and will only aggravate the existing intracellular dehydration

Gastric lavage should be carried out routinely in any patient who is in serious acidosis The dilated stomach of patients with diabetic coma is well known, and the danger of aspirating fluid and producing pulmonary damage has been proved frequently at autopsy The main purpose of the gastric lavage and the enema, however, is to prepare the intestinal tract for the taking of food which would include not merely water and glucose but protein fat, minerals and vitamins

Circulatory stimulants are practically never needed with children and in adults rarely produce any startling effects Norepinephrine may be given intravenously for extreme collapse, but beware of extravasation and resulting gangrene

Blood transfusions have been used rarely in our patients but might be indicated in severe shock It must not be forgotten that in older diabetic patients who may have coronary arteriosclerosis, the rapid increase in blood volume by the use of plasma or whole blood has more than once produced pulmonary edema or cardiac failure

Glucose containing solutions are no longer given in the first hours of the treatment of diabetic coma No one would

argue that the administration of 5 or 10 gms of glucose intravenously, or the giving of glucose after the first six to ten hours when the acute condition had been overcome, will be harmful The plea is against the common practice of giving much larger amounts of glucose from the very beginning of treatment, as if the administration of glucose was itself an essential part of the treatment of coma Glucose itself is entirely inert until it is phosphorylated through the action of insulin When the blood sugar has fallen toward a normal level through the action of insulin, then glucose solutions may be employed with discretion

Potassium Deficiency

Depletion of body reserves of potassium is frequently found in patients with unrecognized or uncontrolled diabetes even without severe acidosis In such cases severe potassium deficiency may be rapidly precipitated by ketosis In some patients the administration of saline solution and an increase in the serum sodium may accentuate potassium depletion as indicated by electrocardiographic changes The striking flattening of T waves, cardiac arrhythmia such as fibrillation muscular weakness and even myocardial failure may result and may occur at a time when the patient s serum CO_2 and sugar are returning to normal 10 to 18 hours after the inauguration of treatment It is wise to follow the administration of potassium solutions with electrocardiograms since hyperpotassemia is as serious as low potassium values

Complications in Coma

Serious hypoglycemia may occur if excessive insulin has been given However, if blood sugar values are followed every three to four hours and if the patient begins to take food in the form of orange juice, oatmeal 10 grams per hour, then hypoglycemia is almost never observed

Renal Failure in Diabetic Acidosis The harmful effect of

diabetic ketosis, whether mild or severe, upon kidney function has long been known Ever since the time of Kulz (1874) the occurrence of many casts, hyaline and granular in the urine sediment, often described as a "shower," has been frequently described Such a shower of casts occurs even in children with severe ketonuria long before drowsiness or unconsciousness may develop In older patients with already damaged kidneys and particularly in patients who have had pyelonephritis, moderate degrees of ketosis may lead rapidly to oliguria With fall in blood pressure and approaching anuria, the urine sediment may even show a good many red cells Oliguria and even anuria represent a most serious development in the course of diabetic ketosis, or various types of oliguria may occur due to various causes

Oliguria and anuria due to dehydration, fall in blood pressure and shock may be regarded as a final stage in the natural history of diabetic coma It may be seen in any patient who has gone through one or two days of severe diabetic acidosis, in which polyuria, ketonuria and the other features of diabetic coma have been present Albuminuria is practically always noted in such patients and may reach a considerable degree in later stages

Acute renal failure may occur early in the course of diabetic ketosis

Infections of the kidney, notably pyelonephritis represent perhaps the most common cause of anuria in diabetic coma A typical case is illustrated by Miss C, clerk, age 38 years who entered the Deaconess Hospital in acidosis with vomiting, Kussmaul respiration and drowsiness on June 26, 1950 Diabetes began in July, 1937, and her first diabetic coma occurred in 1944 with evidence of pyelitis then Her blood pressure had risen steadily following that first coma and in April, 1948, a left nephrectomy was performed because of renal abscesses Within a year following the operation pyuria had developed which had previously been absent. Upon admission in 1950 the urine contained albumin 670 mg, 100

white cells per high power field and she now clearly had renal failure with superimposed diabetic ketosis The blood sugar was 700 mg per 100 cc, plasma CO_2 3 mM and the NPN 110 mg per 100 cc The plasma acetone value was 104 mg per 100 cc, serum potassium 3 85 mEq per liter, serum protein 4 7 per cent With 350 units of insulin in the first hour and one half and another 300 units at the end of the fourth hour, improvement was rapid Her plasma chloride value was 118 mEq, but she nevertheless received 4500 cc of normal saline solution by needle The blood sugar fell steadily toward normal, but the non protein nitrogen fell only slowly during the next few weeks until at the end of two months the non protein nitrogen was 50 mg Her insulin requirement became stabilized at 6 units of crystal line insulin and 50 units of protamine zinc insulin

She returned to the hospital October 4, 1950, for an upper respiratory infection with nausea, vomiting, stupor and edema The blood sugar value was 645 mg, plasma CO_2 2 mM and the NPN value 127 mg The serum potassium was 8 4 mEq and the serum sodium 126 mEq Although the CO_2 value was extremely low no ketone bodies were present in the blood plasma and she was obviously in uremia Although the blood sugar level was readily controlled with insulin, she died in uremia

Anuria may occur in coma complicated by pneumonia or other extra renal infection This type of renal failure is relatively frequent If it can be ascertained that the infection causing associated fever is really extra renal, the outlook may be very much better than when the infection invades the kidneys The treatment of such patients is first an accurate diagnosis and the use of antibiotics directed at the infection Thus cultures in the case of pneumonia or carbuncles may yield organisms resistant to one type of anti biotic or another Errors in the choice of antibiotics may well be disastrous The use of insulin and fluids is according to the general plan of treatment for diabetic ketosis

Neuropathy During and Following Diabetic Coma Various types of neuropathy are seen in patients who have severe forms of diabetic ketosis and coma In patients with previously unrecognized and untreated diabetes it seems that such neuropathy is more apt to be of the severe form However, it is common to find that among patients who have been in uncontrolled diabetic states for weeks or months before actual coma develops, pains in the legs of increasing frequency and severity precede the coma In such patients following ketosis there may be a more severe persistent neuropathy In Table 21 are listed twelve instances of neuropathy Five at least are of exceptional severity The others are less severe Case No 1 with diabetes of 29 years' duration, following diabetic coma developed polyneuritis with extreme weakness and paralysis of the arms with facial weakness which persisted for 6 or 8 months She also had myocardial failure and pleural fluid as well Recovery was incomplete In Case 4 following diabetic coma a polyneuritis with muscular atrophy and paralysis involving both arms and legs required one year for recovery In her case the spinal fluid protein contained was 160 mg per 100 cc during the tide of coma A year later in 1952 she developed pulmonary tuberculosis then hypertension and died in uremia in June, 1954 Case 6 had a complete shoulder girdle paralysis and simulating poliomyelitis However, recovery was complete in 8 months after diabetic coma and with a complete absence of sequelae left no doubt that the original lesion was diabetic neuropathy Case No 9, housewife, age 44 years, with diabetes of 27 years duration, developed, during diabetic coma, severe encephalopathy resembling in some ways poliomyelitis A respirator was required Autopsy performed a few days later showed very marked evidences of neuropathy in the peripheral nerves but more important still in many, many cortical areas Although no hemorrhages were present in the cortex many focal areas of degeneration were present Although

TABLE 21

NEUROPATHY FOLLOWING DIABETIC COMA

Series No	*Case No*	*Sex*	*Age at Onset D M*	*Age at Onset Neuro*	*Nature of Neuropathy and Date*
1	2568	F	7	36	November, 1950 Coma Polyneuritis, paralyses of arms and facial weakness
2	30477	M	17 7	32	Acidosis April 10, 1947—Acidosis Bilateral facial paralysis
3	41733	M	52 9	64	December, 1952 Coma Polyneuritis, severe paresthesiae Pain
4	18550	F	11	26	Coma Polyneuritis, muscular paralyses, 1 year for recovery
5	B8299 19893	F	8	19	September, 1947 Coma Polyneuritis and diarrhea Pain in legs
6	9230	M	19	19	100 lbs June, 1930—Coma Shoulder girdle paralysis Recovery complete 8 months
7	41105	F	39	40	June, 1952 Coma Right ankle drop Left wrist drop Polyneuritis
8	43878	F	17	31	1951—Acidosis Right ankle drop Loss of proprioception
9	B1754 6265	F	17	44	March, 1954 Coma Encephalopathy Sp Fl protein 188 Respirator required
10	24070	F	56 9	57	December, 1943—Coma Polyneuritis —legs Bladder paralysis Pain
11	24695	F	23 6	39	CO_2 7—B S 748 February, 1954—Acidosis Bladder paralysis Severe abdominal pain
12	45002	M	44 5	45 5	August, 1954 Acidosis Unrecognized D M 1 year plus transverse myelitis-like picture with paraplegia—Paralysis of urinary bladder B P 40 to 60 systolic Levofed for 2 days Gangrene with slough. Comatose 3-4 days. Spinal Fluid protein 112 mEq

the spinal fluid protein was normal upon admission it rose to a value of 188 mg during the few days of her encephalopathy On the sixth day the patient was having difficulty in swallowing Deep tendon reflexes had now disappeared *There was increased* generalized weakness, lethargy and difficulty in speaking The pupils were fixed and dilated The blood pressure was labile, tachycardia persistent The serum sodium was low, 119 mEq, potassium 5 5 chlorides 84, the CO_2 22 mEq Two days later the patient was in severe respiratory distress and she was placed in a respirator which was carried out immediately During the next three days until her death her course was one of gradual increasing weakness Case No 12 was sent to the Deaconess Hospital because he had been discovered in diabetic coma in another hospital Upon arrival he was almost pulseless, he required levofed for 2 days He proved to have paraplegia, paralysis of the bladder and this grave and neurologic disorder has persisted for a year Treatment of diabetic neuropathy during ketoacidosis is primarily that of diabetic coma and the metabolic imbalance found The administration of multiple vitamins during the treatment of diabetic coma has become a common practice as a means of ameliorating or preventing neuropathy Whether and to what extent the use of such vitamin preparations is effective can hardly be stated with definiteness or accuracy The treatment of any anemia, accompanying infections of the urinary tract, or circulatory disturbances is essential The prevention of these grave neuropathies obviously depends upon the earlier discovery of diabetes and the prevention of the development of diabetic ketosis and coma in patients who have not previously been treated by adequate dietary and insulin dosage

Causes of Death in Diabetic Acidosis and Coma

Since the patient in diabetic ketosis, drowsy or unconscious, presents real difficulties in the diagnosis of latent or severe complications, it is helpful to bear in mind what actually have been the complications causing death Over the years, among 66 deaths of patients entering the Deaconess Hospital in diabetic coma, about one third died of uncomplicated coma owing to delayed diagnosis and insufficient treatment Sepsis and metastatic infection as with an infected foot or kidney infections or a carbuncle accounted for another third Ten deaths were due to pneumonia Three deaths occurred from pancreatitis In general, then it is serious complications chiefly of an infectious nature which are to be sought in the seriously ill comatose diabetic

The prognosis in diabetic ketosis and coma depends first upon the character of complications In the presence of complications, in and of themselves fatal, such as coronary occlusion and infarction of the heart and carcinomatosis death alone can result In the absence of such hopeless complications, the first factor in the prognosis is the severity of the acidosis Patients in which acidosis is most severe and of longest duration have a more dangerous outlook The totally unconscious patient in whom unconsciousness has lasted for at least twelve hours has a much higher mortality than the patient not yet unconscious Nevertheless the mortality rate in totally unconscious patients has fallen at the Deaconess Hospital from 35 per cent to only 10 3 per cent at present The age of the patient is an important factor About one third of all cases of diabetic coma occurred in children and with them the advantage of youth gives a vastly better prognosis than when diabetic coma occurs in the aged patient of long duration, particularly in the presence of cardio vascular complications

It should be emphasized that patients in whom acidosis may not be far advanced often have a very grave prognosis owing to the presence of severe infection Any degree of diabetic ketosis, therefore, must be taken seriously This is all the more important in view of the follow-up of patients who have had severe diabetic ketosis or coma It has long been known that patients who recover from diabetic coma are very prone to the development of pulmonary tuberculosis during the next 5-7 years Today, however, patients who have had diabetic ketosis of mild or severe degrees on more than one occasion show a particularly high incidence of the cardiovascular complication commonly most frequent in the form of diabetic nephropathy One may analyze causes of death in 180 patients after recovery from coma Here the striking difference between the earlier periods from 1923 1946 and later periods from 1946-1953 stands out prominently Thus, the diabetic nephropathy was not recorded as a cause of death in patients after discharge from the hospital in the earlier periods, but it actually was present as a cause of death in 43 out of 113 deaths for the period from 1946 1953 Recurrent diabetic coma was a cause of death in only 10 out of 113 Cardiac deaths numbered 24, tuberculosis only 7 and miscellaneous causes accounted for 29 deaths

Prevention

The prevention of diabetic coma depends first upon the detection of diabetes in an early stage of the disease In the last 20 years at the Deaconess Hospital, although the percentage has varied somewhat from year to year, from 12 15 per cent of all the patients who arrived in diabetic coma did not know of their diabetes until acidosis developed The detection of diabetes in an early and favorable stage will be brought about when all doctors routinely test the urine of every patient seen, when the diabetes detection drives sponsored by the American Diabetes Association are accepted

and when every person in the country has the urine tested for sugar periodically The discovery of diabetes is only the first step however because once the diabetic patient knows he has diabetes it is essential that his instruction and training be thorough in respect to diabetic acidosis He must understand first the factors which produce diabetic acidosis and coma second the speed with which acidosis may develop third the variety of symptoms which may be early manifestations of diabetic ketosis Earlier clinical diagnoses and more adequate provisions for prompt and aggressive treatment must be provided

Patients should be aware that diabetes is a chronic and not a temporary disorder The patient should be instructed as to the favorable course which diabetes may take under adequate treatment and control Conversely the patient should also realize how rapidly cyclonic changes can come on with acute infection and other complications Many patients cease to test their urine daily feeling that they only need to do it when they are feeling badly Most important of all patients must learn not to omit insulin merely because they are unable to take food because of some acute infection Unfortunately doctors have in their zeal to prevent hypoglycemia not rarely instructed patients to give *up insulin at the very time when in early acidosis it was* most effective Insulin should never be given up unless the urine tests are and remain sugar free

CHAPTER IX

TUBERCULOSIS AND DIABETES

In the association of the two diseases, diabetes and tuberculosis, the patient with diabetes has increased susceptibility to tuberculosis but the patient with tuberculosis does not appear to have increased susceptibility to diabetes Among Joslin Clinic patients, diabetes antedated tuberculosis in 85 per cent

Incidence

The total incidence of latent tuberculosis, revealed by careful surveys, is far greater in diabetic individuals than in the general population Thus, 2 8 per cent tuberculous patients were revealed in a survey of well diabetics in contrast to 0 1 per cent tuberculous patients revealed in a survey of the entire population The tuberculous sensitive part of the diabetic population includes the juvenile patient where the susceptibility is 10 times that of the general population, the adolescent where the greatest frequency is found, namely, 20 times that of the general population the male rather than the female and the diabetic patient who has had bouts of diabetic coma Thus within three years of an attack of diabetic coma, 1 in 12 of the diabetic patients at the Joslin Clinic has shown signs of pulmonary tuberculosis

The falling incidence of tuberculosis in autopsies reflects improvement in the treatment of both diseases In 1883 Bouchardat found tuberculosis in all diabetic patients at autopsy His explanation for the susceptibility is interesting He drew a parallel between the polyuria of diabetes and the

lactating cow and observed coincidentally with grazing in the latter when there was no lactation, there was no tuberculosis When the animals were not grazing, but in a barn and lactating, then there was tuberculosis The relative state of dehydration in the animal he compared with the dehydration in diabetes and their coincidental tuberculosis

Tuberculosis is still an important part of our problem, for in juvenile patients it is the third cause of death and in the adult the fourth cause of death Thus, in the juvenile population the causes in order of importance are arteriosclerotic renal disease, second, coma, and third, tuberculosis, in the adult patient, first, arteriosclerosis, second, cancer, third, coma, and fourth tuberculosis

It is natural to ask what are the factors in diabetes influencing the increased susceptibility to the tubercle bacillus Susceptibility does not appear to be due to a lack of natural immunity In the pre diabetic state there is a high incidence of calcification in the tracheobronchial lymph nodes In fact, 75 per cent of our patients have shown this characteristic It has been found too in those diabetic patients who have contracted tuberculosis Therefore, native and acquired immunity did not seem to protect the individual There are three logical explanations which suggest themselves First, the growth of the tubercle bacillus is favored in diabetes, second, virulence is increased, and third, the defense against tubercle bacillus is lowered Known changes in fluid and tissue chemistry of diabetes suggest that any one or all of these may be contributing factors Thus, dehydration alone may be an important factor for the tubercle bacillus will not grow if covered with a film of water Acidosis is also a factor, for the best growth for the tubercle bacillus is in a hydrogen ion concentration of 6 4 to 7 8 Protein catabolism, too, which we would find in uncontrolled diabetes may be very important, for amino acids are the source of nitrogen for the tubercle bacillus Fat catabolism is a possibility, for glycerol is the sole source of

carbohydrate for this organism Hyperglycemia itself may contribute, for the growth of tubercle bacillus parallels sugar utilization

Virulence is increased in acid media Again we would correlate this with uncontrolled diabetes and bouts of ketoacidosis

Loss of protection from the reticuloendothelial system is suggested, because especially in ketoacidosis these cells become distended with fat and their ability to phagocytose and encapsulate the organism may be impaired

Pathology

The microscopic appearance of tuberculosis lesions in the diabetic are the same as in the general population Differences occur more in relation to frequency of certain forms age susceptibility, and prognosis Thus, at the Deaconess Hospital the frequency of the lesions in tuberculous patients was as follows apical involvement, 100 per cent, caseation 70 per cent, cavitation, 60 per cent, pneumonic forms, 20 per cent, healed 7 per cent, miliary, 7 per cent, non sensitized and overwhelming infections, 6 per cent

From the foregoing it is evident that healing spontaneously has not been common, though possible Caseation and cavitation have been frequent The pneumonic forms are not so common as previously thought, miliary tuberculosis is extremely uncommon, and the lesions similar to those found in the Negro population are common

Involvement of the pancreas has not been observed and involvement of the meninges, liver, spleen kidney, adrenals, bone and peritoneum also has been rare It is possible that the pancreas has local immunity because lipase may dissolve the fatty envelope

Symptoms and Signs

The most important factor in etiology of clinical tuberculosis is, of course, exposure The clinical course is insidious

for the disease is rarely revealed early by clinical symptoms Weight loss, however, may be excessive The average for Joslin Clinic patients was 45 pounds and the range 19 75 A fallacy exists that the lesions are more silent It is true that hemoptysis and pleural effusion are rare, but weight loss, fever, productive cough and sweating, as well as malaise, lassitude and fatigue occur Though not common, atelectasis and spontaneous pneumothorax have been observed Such signs as dullness and râles are as typical or atypical in the diabetic as they are of the general population

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The frequency of positive sputum parallels good technique Concentration of the specimen, selected source and cultures favor the positive diagnosis especially if bronchoscopic technique is used

Treatment of Tuberculosis

Though healing spontaneously is possible, in the past before the days of modern chemotherapy and antibiotics the mortality in the diabetic population from tuberculosis was as high as 94 per cent The duration of life was short, on the average 5 5 years

The medical treatment for tuberculosis in diabetes is essentially the same as in the general population—bed rest and the combination of chemotherapy and antibiotic therapy, streptomycin and para amino salicylic acid (SM PAS), the dose schedule being 1 gm of SM given daily in a single dose plus 12 grams of PAS in three divided doses In addition isonicotinic acid hydrazide (INH) has been employed usually along with streptomycin and para aminosalicylic acid in a dose range of 150-300 mg It must be remembered that peripheral neuropathy is noted in ₚ

CHAPTER X

URINARY TRACT INFECTIONS

Frequency and Types of Infection

Urinary tract infections occur frequently in uncontrolled diabetics The incidence at autopsy may well be 30 per cent The common infections are E coli, staphylococcus aureus, staphylococcus albus, proteus vulgaris, streptococcus hemolyticus, streptococcus faecalis, aerobacter aerogenes, pseudomonas aeruginosa or often a mixed infection So important are these infections to the future of diabetics, especially the younger group of patients, that minimal evidence of urinary tract infection is given maximal diagnostic and therapeutic attention Thus, if a clean voided specimen contains 10 12 white blood cells, a catheter specimen is recommended for sediment culture and sensitivity and the appropriate chemotherapy prescribed

(A) *Types a Retrograde, b Metastatic* The evidence in our patients has been overwhelming that *the root of infection is* most commonly retrograde, associated with such lesions as urethrostenosis, urethropolyps, polyps of the bladder, diverticuli, stones, bladder uretero or renal, and/or ureterostenosis With the susceptibility of the diabetic's skin to infection, a metastatic origin *is not uncommon* When the diagnosis of pyelonephritis has been suspected by the urine sediment, an intravenous pyelogram is recommended and a retrograde pyelogram if indicated

c Cystitis and Perinephric Abscess The female diabetic patient *is* particularly *susceptible to pyelonephritis* and also

to cystitis, the management of which is essentially the same as that of pyelitis

Formerly perinephric abscess was a common complication in diabetic patients Today with the early use of appropriate antibiotic or chemotherapeutic agents the condition occurs infrequently

Necrotizing Papillitis

A severe form of pyelonephritis, necrotizing papillitis, has received considerable attention lately This condition is usually fulminating and often rapidly fatal It is usually found in uncontrolled diabetic patients and is characterized histologically by almost complete destruction of the papillae with an ascending involvement of the renal parenchyma The casts of papillae can be identified in the urine The condition can sometimes be suspected by the profound general reaction out of proportion to the degree of clinical pyelonephritis The patients lapse into a comatose state rapidly The clinical picture is characterized by azotemia and renal shutdown Antibiotic and chemotherapeutic agents administered intravenously must be pushed in these cases Although in many the diagnosis is made postmortem, in one case at the Deconess Hospital, nephrectomy disclosed unilateral necrotizing papillitis and the patient recovered

Neuropathic Bladder

Paralysis of the bladder is a distressing complication of diabetes It appears to be part of the picture of diabetic neuropathy It is characterized by high volume residual urine, as much as one or more liters In addition to good chemical control of diabetes, eradication of co-existing infection, supportive care in the form of vitamins, tidal drainage or surgical procedure may be tried in these patients

The main principals of management of urinary tract infections in the diabetic include the following Prevention by the best possible chemical control of diabetes, instruction of female patients in the elements of hygiene and prompt treatment of such foci of infection as abscesses and carbuncles, identification of the infecting organism and the use of the appropriate chemotherapeutic agents or antibiotic, and careful followup of these patients at 2-4 week intervals with repeated catheter specimens, cultures and sensitivity tests

Treatment of infections of the urinary tract include the use of sulfonamide for gram negative, penicillin for gram positive organisms, erythromycin for resistant gram positive streptomycin for resistant gram negative, and finally the use of aureomycin, terramycin, and chloramphenicol in combination for the most resistant type of infection

CHAPTER XI

TREATMENT OF SKIN COMPLICATIONS

Because the skin is involved in carbohydrate metabolism, dermatological complications are associated with diabetes. A suggested classification of skin lesions according to their etiology is as follows:

1. Lesions due to insulin treatment
2. Lesions due to dietary treatment
3. Metabolic lesions
4. Lesions where susceptibility is increased because of diabetes
5. Lesions where the seriousness is increased because of diabetes
6. Lesions concerned with the etiology of diabetes
7. Dermatological diabetes

The skin lesions caused by insulin include four:

1. Allergies
2. Insulin hypertrophy
3. Insulin atrophy
4. Insulin abscesses

Allergies due to insulin include local urticaria, generalized urticaria, angioneurotic edema as well as lesions associated with gastrointestinal upsets, purpura and anaphylactic shock. *The possible causes of insulin allergies are multiple.* They may be due to the protein of insulin itself, to impurities in the preparation due to the animal origin of

insulin, or to the foreign protein added to globin or protamine insulin Local urticaria is the most common manifestation It occurs in the majority of patients but is usually self corrected This spontaneous desensitization occurs some 3-4 weeks after insulin therapy has been inaugurated Severe cases, however, require special treatment The simplest forms of treatment include the use of antihistamines which may be administered orally or mixed with insulin. Another simple way of controlling insulin allergy of the urticarial type is the use of "special' insulin Still another technique is the administration of insulin intramuscularly instead of subcutaneously Dolger has suggested that in the allergic patient regular insulin may be boiled and that after a period of three to four weeks use of boiled insulin, the ordinary type may be substituted Recrystallization of insulin to an extraordinarily pure degree may solve the problem of some patients

Desensitization is necessary in the severest of these cases and the following schedule has proved to be useful On the first day four doses of insulin may be given in the following strengths 1/1000 of a unit, 1/500, 1/250 and 1/125 On the second day 1/100, 1/50, 1/25 and 1/12 On the third day 1/5, 1/2, 1 and 2 and on the next day 4, 5, 6 and 7 units The original preparations may be prepared in the following fashion 4 units of insulin in 40 cc of normal salt solution, 1 cc of this may be diluted with 9 cc of salt solution, 1/1000 of a unit will then be 1/10 cc of this preparation Another method is to desensitize with histamine itself

Perhaps one of the most marked manifestations of insulin allergy is resistance to insulin The majority of patients requiring over 1000 units of insulin a day demonstrate insulin antibodies The seriousness of starting insulin and stopping it cannot be overemphasized For this reason we have adopted the practice of recommending that patients continue with insulin as infrequently as two doses per week

Insulin Lipodystrophy

Insulin lipodystrophies are of two types hypertrophy of the fat tissue and atrophy of the fat tissue The majority of the cases of hypertrophy occur in males, with a ratio of 2 to 1, but atrophy is found mostly in children and women Of general interest in the problem of insulin atrophies are the following facts The fat which disappears is neutral fat No inflammatory reactions are observed They result from any type of insulin and the pH of the insulin does not appear to be important

The incidence of atrophies in adult females is 22 per cent in contrast to 3 per cent in adult males The difference is correlated with the greater lipolytic activity of the female Histological section of the hypertrophied areas shows the heavy deposition of fat in which the fat cells are individually large and contain a deposition of glycogen

Treatment of either consists of the selection for the site of the administration of insulin and adequate distribution of sites Atrophy due to insulin therapy has been described at, near to, or even remote from the site of injection Its greatest significance is a cosmetic one Reassurance is perhaps the best therapy, for these lesions tend to disappear between 2 and 8 years after their first appearance Prevention is suggested by the wide selection of sites and choice of sites which are of the least cosmetic importance Therefore, high thigh, buttocks and lower abdomen are the sites of choice for diabetic women and diabetic children Duncan has emphasized the fact that cold insulin is a possible cause of insulin atrophy and has recommended that the bottle of insulin in current use should be kept at room temperature Collens recommends re injection into atrophied areas since the atrophy does not involve muscle tissue but only subcutaneous fat The administration of insulin intramuscularly may be recommended for those persons for whom the prob-

lem is most serious Insulin has been mixed with hyaluronidase These preparations must be made freshly daily Their use is not practical for home therapy The local use of androgenic ointment has also been suggested for the male diabetic patient

Dietary Lesions

The skin lesions which are associated with diet prescriptions include xanthosis and the growth of lanugo hair Both of these conditions were seen commonly in the days of undernutrition and prior to 1936 Lanugo hair is uncommon today Xanthosis, however, is still found in the younger part of the diabetic population Levels of blood carotene and cholesterol are elevated This lesion is characterized by the deep yellow to orange color of the nasolabial fold the plantar and palmar surfaces The condition is believed to be due not only to the excess of carotene in the diet, but also the failure of the diabetic to utilize carotene Therapy consists of omission of the highly pigmented vegetables yellow and green, such as carrots and peas, and also egg yolk and butter The condition is benign but sometimes causes confusion in the differential diagnosis of hepatitis Formerly when diabetic children showed hepatomegaly and xanthosis, hepatitis was often suspected The prognosis for recovery from these conditions is excellent

Metabolic

Metabolic skin lesions include xanthomata and necrobiosis lipoidica diabeticorum Xanthomata may be divided into three groups—palpebrarum tuberosum and diabeticorum. Xanthoma palpebrarum has been observed more frequently in diabetics than in the general population Thus 1.5 per cent of diabetics examined have shown this lesion in contrast to 0 8 per cent of the control non diabetic group The histopathology of the lesion consists of lipid laden histocytes

There is no known medical treatment for this condition, which if disfiguring, necessitates surgical excision Xanthoma tuberosum occurs both in diabetics and non-diabetics The condition is familial and histopathologically is characterized by lipoid containing macrophages Medical treatment for this condition is now successful for the lesions will disappear with the administration of heparin

Xanthoma diabeticorum is characterized by the appearance of golden papules on a rose base, most frequently on the extensor surfaces of the body They vary in size but are usually about 5 mm in diameter Again, the histopathological findings consist of the lipid laden macrophages This condition occurs most often when the cholesterol of the blood has risen to the level of 500 mg or more

The control of diabetes by insulin and careful selection of the diet will facilitate the disappearance of these lesions Thus, the choice of fats which are derived from vegetables rather than those of animal origin should be emphasized. Eggs, dairy products and glandular meats favor elevation of serum values for cholesterol. The prognosis for recovery from this lesion is excellent It is occasionally seen in association with lipemia retinalis

Necrobiosis lipoidica diabeticorum is perhaps the most characteristic of the diabetic lesions It was first described by Oppenheimer in 1928 and named by Urbach in 1932 Nine out of every ten individuals with necrobiosis have diabetes The one out of ten without clinical diabetes usually proves to be a subclinical diabetic The lesion is recognized as one of the pre diabetic signs This skin complication has five characteristic phases. The first, macular, consists of a slightly reddish macular papillar area Patients frequently associate it with trauma and often confuse it with insect bites In the second stage, violacious, the lesion takes on a deep angry purplish color then changes to a third stage, the plaque, with sharply defined elevated borders In addition,

the color now becomes a salmon pink There are yellow areas of fat deposit and tiny blood vessels traverse the lesion. Then a typical fourth ulcerative stage occurs The central part of the lesion becomes depressed It is covered with a tense shiny membrane which looks like cellophane and finally a fifth stage, which is not usually described in the literature, is that of an inconspicuous scar The vivid color disappears and sometimes it is almost impossible to dis cover the past site of the lesion This progression from the macule to the scar is slow, often covering a whole decade or more

Histopathologically, the condition is an endarteritis with fatty degeneration of connective tissue There is degenera tion of collagen fibers, loss of elastic tissue, perivascular in flammation with connective tissue cells—histocytes, lym phocytes, leukocytes and plasma cells, obliteration of the small blood vessels, extracellular deposit of fat with a high phospholipid and free cholesterol content The frequency in the general diabetic population is 1 per 400 and in the juvenile population 1 in 50 Fifty five per cent of all cases occur with patients whose diabetes onset was in childhood and two thirds occur in females. The age at which the lesion has been recognized has varied in our series from 6-70 years Nearly two thirds have had hypercholesteremia one fifth hepatomegaly, 30 per cent have had coma, 64 per cent had other vascular manifestations, and 71 per cent diabetic retinopathy

Surgical removal is not recommended The lesions often disappear during pregnancy The prognosis for recovery, although slow, is excellent The lesions have been mistaken *for lues, tuberculosis and malignancy* The importance is largely a cosmetic one The distribution is usually in the lower extremities in relation to the malleoli but these *lesions have been observed* also on the arms abdomen, thighs and even on the face

Increased Susceptibility Because of Diabetes

The diabetic is particularly susceptible to pyogenic infections of the skin such as abscesses to which the injection of insulin makes them somewhat more susceptible Jumbo carbuncles, cellulitis, impetigo and furuncles are due to staphylococcus infection The reason for the increased susceptibility to such infections is not completely clear, but loss of glucose and dehydration have been considered possibilities With modern antibiotics and chemotherapy these lesions are readily controlled Penicillin may be used for gram + and erythromycin for resistant gram + organisms Control of diabetes is stressed Prevention is sought by such detergents as phisoderm

Pruritus pudendi is most often due to monilia infection involving the vulval mucous membranes, the specific treatment of which was formerly gentian violet It should be applied infrequently, once daily in strengths not greater than 1 per cent Mysticlin is favored at present

The following lesions become important because of existing diabetes epidermophytosis, warts, corns, calluses, hirsutism, dermatitis gangrenosa and Dupuytren's contracture The usual methods for treating epidermophytosis may be used, but the selection of the milder forms of therapy is stressed These are 1 4000 solution of potassium permanganate, 1% aqueous aluminum acetate, half strength Whitfield's ointment The following directions are printed for our patients Because the occurrence of interdigital fissures these lesions may be the portal of entry for staphylococci and eventually cause osteomyelitis

SPECIAL DIRECTIONS TO THE PATIENT
REGARDING CARE OF THE FEET

Many people are affected with itching scaling cracking or blisters on the feet especially between the toes This condition is often a ringworm infection or epidermophytosis as it is called, and is caused

carbohydrate for this organism Hyperglycemia itself may contribute, for the growth of tubercle bacillus parallels sugar utilization ✓

Virulence is increased in acid media Again we would correlate this with uncontrolled diabetes and bouts of keto acidosis

Loss of protection from the reticuloendothelial system is suggested because especially in ketoacidosis these cells be come distended with fat and their ability to phagocytose and encapsulate the organism may be impaired

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From the foregoing it is evident that healing spontane ously has not been common, though possible Caseation and cavitation have been frequent The pneumonic forms are not so common as previously thought, miliary tuberculosis is extremely uncommon, and the lesions similar to those found in the Negro population are common

Involvement of the pancreas has not been observed and involvement of the meninges, liver, spleen, kidney, adrenals, bone and peritoneum also has been rare It is possible that the pancreas has local immunity because lipase may dis solve the fatty envelope

Symptoms and Signs

The most important factor in etiology of clinical tubercu losis is, *of course, exposure* The clinical course is insidious

for the disease is rarely revealed early by clinical symptoms Weight loss however, may be excessive The average for Joslin Clinic patients was 45 pounds and the range 19 75 A fallacy exists that the lesions are more silent It is true that hemoptysis and pleural effusion are rare, but weight loss, fever, productive cough and sweating, as well as malaise, lassitude and fatigue occur Though not common, atelecta sis and spontaneous pneumothorax have been observed Such signs as dullness and râles are as typical or atypical in the diabetic as they are of the general population

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The frequency of positive sputum parallels good technique Concentration of the specimen, selected source and cultures favor the positive diagnosis especially if broncho scopic technique is used

Treatment of Tuberculosis

Though healing spontaneously is possible, in the past before the days of modern chemotherapy and antibiotics the mortality in the diabetic population from tuberculosis was as high as 94 per cent The duration of life was short, on the average 5 5 years

The medical treatment for tuberculosis in diabetes is essentially the same as in the general population—bed rest and the combination of chemotherapy and antibiotic therapy, streptomycin and para amino-salicylic acid (SM PAS), the dose schedule being 1 gm of SM given daily in a single dose plus 12 grams of PAS in three divided doses In addition, isonicotinic acid hydroxide (INH) has been employed usually along with streptomycin and para amino-salicylic acid *in a dose range of 150-300 mg It must be* remembered that peripheral neuropathy is noted in patients

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Loss of protection from the reticuloendothelial system is suggested, because especially in ketoacidosis these cells become distended with fat and their ability to phagocytose and encapsulate the organism may be impaired

Pathology

The microscopic appearance of tuberculosis lesions in the diabetic are the same as in the general population Differences occur more in relation to frequency of certain forms, age susceptibility, and prognosis Thus, at the Deaconess Hospital the frequency of the lesions in tuberculous patients was as follows apical involvement, 100 per cent, caseation, 70 per cent, cavitation, 60 per cent, pneumonic forms, 20 per cent, healed, 7 per cent, miliary, 7 per cent, non sensitized and overwhelming infections, 6 per cent

From the foregoing it is evident that healing spontaneously has not been common, though possible Caseation and cavitation have been frequent The pneumonic forms are not so common as previously thought, miliary tuberculosis is extremely uncommon, and the lesions similar to those found in the Negro population are common

Involvement of the pancreas has not been observed and involvement of the meninges, liver, spleen kidney, adrenals, bone and peritoneum also has been rare It is possible that the pancreas has local immunity because lipase may dissolve the fatty envelope

Symptoms and Signs

The most important factor in etiology of clinical tuberculosis is, of course, exposure The clinical course is insidious

to cystitis, the management of which is essentially the same as that of pyelitis

Formerly perinephric abscess was a common complication in diabetic patients Today with the early use of appropriate antibiotic or chemotherapeutic agents the condition occurs infrequently

Necrotizing Papillitis

A severe form of pyelonephritis, necrotizing papillitis, has received considerable attention lately This condition is usually fulminating and often rapidly fatal It is usually found in uncontrolled diabetic patients and is characterized histologically by almost complete destruction of the papillae with an ascending involvement of the renal parenchyma The casts of papillae can be identified in the urine The condition can sometimes be suspected by the profound general reaction out of proportion to the degree of clinical pyelonephritis The patients lapse into a comatose state rapidly The clinical picture is characterized by azotemia and renal shutdown Antibiotic and chemotherapeutic agents administered intravenously must be pushed in these cases Although in many the diagnosis is made postmortem, in one case at the Deconess Hospital nephrectomy dis closed unilateral necrotizing papillitis and the patient recovered

Neuropathic Bladder

Paralysis of the bladder is a distressing complication of diabetes It appears to be part of the picture of diabetic neuropathy It is characterized by high volume residual urine, as much as one or more liters In addition to good chemical control of diabetes, eradication of co-existing in fection supportive care in the form of vitamins, tidal drain age or surgical procedure may be tried in these patients

CHAPTER X

URINARY TRACT INFECTIONS

Frequency and Types of Infection

Urinary tract infections occur frequently in uncontrolled diabetics The *incidence at autopsy may well be 30 per* cent The common infections are E coli, staphylococcus aureus, staphylococcus albus, proteus vulgaris, streptococcus hemolyticus, streptococcus faecalis, aerobacter aerogenes, pseudomonas aeruginosa or often a mixed infection So important are these infections to the future of diabetics especially the younger group of patients, that minimal evidence of urinary tract *infection is given maximal diagnostic* and therapeutic attention Thus, if a clean voided specimen contains 10-12 white blood cells, a catheter specimen is recommended for sediment culture and sensitivity and the appropriate chemotherapy prescribed

(*A*) *Types a Retrograde, b Metastatic* The evidence in our patients has been overwhelming that the root of infection is most commonly retrograde, associated with such lesions as urethrostenosis, urethropolyps, polyps of the bladder, diverticuli, stones, bladder-uretero or renal, and/or ureterostenosis With the susceptibility of the diabetic's skin to infection, a metastatic origin is not uncommon When *the diagnosis of pyelonephritis has been* suspected by the urine sediment, an intravenous pyelogram is recommended and a retrograde pyelogram if indicated

c Cystitis and Perinephric Abscess The female diabetic patient is particularly susceptible to pyelonephritis and also

CHAPTER XI

TREATMENT OF SKIN COMPLICATIONS

Because the skin is involved in carbohydrate metabolism, dermatological complications are associated with diabetes. A suggested classification of skin lesions according to their etiology is as follows

1. Lesions due to insulin treatment
2. Lesions due to dietary treatment
3. Metabolic lesions
4. Lesions where susceptibility is increased because of diabetes
5. Lesions where the seriousness is increased because of diabetes
6. Lesions concerned with the etiology of diabetes
7. Dermatological diabetes

The skin lesions caused by insulin include four

1. Allergies
2. Insulin hypertrophy
3. Insulin atrophy
4. Insulin abscesses

Allergies due to insulin include local urticaria, generalized urticaria, angioneurotic edema as well as lesions associated with gastrointestinal upsets, purpura and anaphylactic shock. The possible causes of insulin allergies are multiple. They may be *due to the protein of insulin itself, to impurities* in the preparation due to the animal origin of

The main principals of management of urinary tract infections in the diabetic include the following Prevention by *the best possible chemical control of diabetes*, instruction of female patients in the elements of hygiene and prompt treatment of such foci of infection as abscesses and carbuncles, identification of the infecting organism and the use of the appropriate chemotherapeutic agents or antibiotic, and careful followup of these patients at 2-4 week intervals with repeated catheter specimens, cultures and sensitivity tests

Treatment of infections of the urinary tract include the use of sulfonamide for gram negative, penicillin for gram positive organisms, erythromycin for resistant gram positive,[14] *streptomycin for resistant gram negative*, and finally the use of aureomycin, terramycin, and chloramphenicol in combination for the most resistant type of infection

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insulin, or to the foreign protein added to globin or protamine insulin Local urticaria is the most common manifestation It occurs in the majority of patients but is usually self-corrected This spontaneous desensitization occurs some 3 4 weeks after insulin therapy has been inaugurated Severe cases, however, require special treatment The simplest forms of treatment include the use of antihistamines which may be administered orally or mixed with insulin Another simple way of controlling insulin allergy of the urticarial type is the use of 'special insulin Still another technique is the administration of insulin intramuscularly instead of subcutaneously Dolger has suggested that in the allergic patient regular insulin may be boiled and that after a period of three to four weeks use of boiled insulin the ordinary type may be substituted Recrystallization of insulin to an extraordinarily pure degree may solve the problem of some patients

Desensitization is necessary in the severest of these cases and the following schedule has proved to be useful On the first day four doses of insulin may be given in the following strengths 1/1000 of a unit, 1/500, 1/250 and 1/125 On the second day 1/100, 1/50, 1/25 and 1/12 On the third day 1/6, 1/2, 1 and 2 and on the next day 4 5, 6 and 7 units The original preparations may be prepared in the following fashion 4 units of insulin in 40 cc of normal salt solution, 1 cc of this may be diluted with 9 cc of salt solution, 1/1000 of a unit will then be 1/10 cc of this preparation Another method is to desensitize with histamine itself

Perhaps one of the most marked manifestations of insulin allergy is resistance to insulin The majority of patients requiring over 1000 units of insulin a day demonstrate insulin antibodies The seriousness of starting insulin and stopping it cannot be overemphasized For this reason we have adopted the practice of recommending that patients continue with insulin as infrequently as two doses per week

Insulin Lipodystrophy

Insulin lipodystrophies are of two types hypertrophy of the fat tissue and atrophy of the fat tissue The majority of the cases of hypertrophy occur in males, with a ratio of 2 to 1, but atrophy is found mostly in children and women Of general interest in the problem of insulin atrophies are the following facts The fat which disappears is neutral fat No inflammatory reactions are observed They result from any type of insulin and the *p*H of the insulin does not appear to be important

The incidence of atrophies in adult females is 22 per cent in contrast to 3 per cent in adult males The difference is correlated with the greater lipolytic activity of the female Histological section of the hypertrophied areas shows the heavy deposition of fat in which the fat cells are individually large and contain a deposition of glycogen

Treatment of either consists of the selection for the site of the administration of insulin and adequate distribution of sites Atrophy due to insulin therapy has been described at, near to, or even remote from the site of injection Its greatest significance is a cosmetic one Reassurance is perhaps the best therapy, for these lesions tend to disappear between 2 and 8 years after their first appearance Prevention is suggested by the wide selection of sites and choice of sites which are of the least cosmetic importance Therefore, high thigh, buttocks and lower abdomen are the sites of choice for diabetic women and diabetic children Duncan has emphasized the fact that cold insulin is a possible cause of insulin atrophy and has recommended that the bottle of insulin in current use should be kept at room temperature Collens recommends re injection into atrophied areas since the atrophy does not involve muscle tissue but only subcutaneous fat The administration of insulin intramuscularly may be recommended for those persons for whom the prob-

lem is most serious Insulin has been mixed with hyaluronidase These preparations must be made freshly daily Their use is not practical for home therapy The local use of androgenic ointment has also been suggested for the male diabetic patient

Dietary Lesions

The skin lesions which are associated with diet prescriptions include xanthosis and the growth of lanugo hair Both of these conditions were seen commonly in the days of undernutrition and prior to 1936 Lanugo hair is uncommon today Xanthosis however is still found in the younger part of the diabetic population Levels of blood carotene and cholesterol are elevated This lesion is characterized by the deep yellow to orange color of the nasolabial fold the plantar and palmar surfaces The condition is believed to be due not only to the excess of carotene in the diet but also the failure of the diabetic to utilize carotene Therapy consists of omission of the highly pigmented vegetables yellow and green such as carrots and peas and also egg yolk and butter The condition is benign but sometimes causes confusion in the differential diagnosis of hepatitis Formerly when diabetic children showed hepatomegaly and xanthosis hepatitis was often suspected The prognosis for recovery from these conditions is excellent

Metabolic

Metabolic skin lesions include xanthomata and necrobiosis lipoidica diabeticorum Xanthomata may be divided into three groups—palpebrarum tuberosum and diabeticorum Xanthoma palpebrarum has been observed more frequently in diabetics than in the general population Thus 1 5 per cent of diabetics examined have shown this lesion in contrast to 0 8 per cent of the control non diabetic group The histopathology of the lesion consists of lipid laden histocytes

There is no known medical treatment for this condition, which if disfiguring, necessitates surgical excision Xanthoma tuberosum occurs both in diabetics and non-diabetics The condition is familial and histopathologically is characterized by lipoid containing macrophages Medical treatment for this condition is now successful for the lesions will disappear with the administration of heparin

Xanthoma diabeticorum is characterized by the appearance of golden papules on a rose base, most frequently on the extensor surfaces of the body They vary in size but are usually about 5 mm in diameter Again the histopathological findings consist of the lipid laden macrophages This condition occurs most often when the cholesterol of the blood has risen to the level of 500 mg or more

The control of diabetes by insulin and careful selection of the diet will facilitate the disappearance of these lesions Thus the choice of fats which are derived from vegetables rather than those of animal origin should be emphasized. Eggs dairy products and glandular meats favor elevation of serum values for cholesterol The prognosis for recovery from this lesion is excellent. It is occasionally seen in association with lipemia retinalis

Necrobiosis lipoidica diabeticorum is perhaps the most characteristic of the diabetic lesions It was first described by Oppenheimer in 1928 and named by Urbach in 1932 Nine out of every ten individuals with necrobiosis have diabetes The one out of ten without clinical diabetes usually proves to be a subclinical diabetic The lesion is recognized as one of the pre-diabetic signs This skin complication has five characteristic phases The first, macular, consists of a slightly reddish macular papillar area Patients frequently associate it with trauma and often confuse it with insect bites In the second stage, violacious, the lesion takes on a deep angry purplish *color then changes to a third stage, the* plaque, with sharply defined elevated borders In addition,

the color now becomes a salmon pink There are yellow areas *of fat deposit and tiny blood vessels traverse the lesion.* Then a typical fourth ulcerative stage occurs The central part of the lesion becomes depressed *It is covered with a* tense shiny membrane which looks like cellophane and finally a fifth stage, which is not usually described in the literature, is that of an inconspicuous scar The vivid color disappears and sometimes it is almost impossible to discover the past site of the lesion This progression from the macule to the scar is slow, often covering a whole decade *or more*

Histopathologically, the condition is an endarteritis with fatty degeneration of connective tissue There is degeneration of collagen fibers, loss of elastic tissue, perivascular inflammation with connective tissue cells—histocytes, lymphocytes, leukocytes and plasma cells, obliteration of the small blood vessels, extracellular deposit of fat with a high phospholipid and free cholesterol content *The frequency* in the general diabetic population is 1 per 400 and in the juvenile population 1 in 50 Fifty five per cent of all cases occur with patients whose diabetes onset was in childhood and two thirds occur in females The age at which the lesion has been recognized has varied in our series from 6 70 years Nearly two thirds have had hypercholesterinemia, one-fifth hepatomegaly, 30 per cent have *had coma,* 64 per cent had other vascular manifestations, and 71 per cent *diabetic retinopathy*

Surgical removal is not recommended The lesions often disappear during pregnancy The prognosis for recovery, although slow, is excellent The lesions have been mistaken for lues, tuberculosis and malignancy The importance is largely a cosmetic one The distribution *is usually* in the lower extremities in relation to the malleoli but these *lesions have been observed* also on the arms, abdomen, thighs and even on the face

Increased Susceptibility Because of Diabetes

The diabetic is particularly susceptible to pyogenic infections of the skin such as abscesses to which the injection of insulin makes them somewhat more susceptible Jumbo carbuncles, cellulitis, impetigo and furuncles are due to staphylococcus infection The reason for the increased susceptibility to such infections is not completely clear, but loss of glucose and dehydration have been considered possibilities With modern antibiotics and chemotherapy these lesions are readily controlled Penicillin may be used for gram + and erythromycin for resistant gram + organisms Control of diabetes is stressed Prevention is sought by such detergents as phisoderm

Pruritus pudendi is most often due to monilia infection involving the vulval mucous membranes, the specific treatment of which was formerly gentian violet It should be applied infrequently, once daily in strengths not greater than 1 per cent Mysticlin is favored at present

The following lesions become important because of existing diabetes epidermophytosis, warts, corns, calluses, hirsutism, dermatitis gangrenosa and Dupuytren's contracture The usual methods for treating epidermophytosis may be used, but the selection of the milder forms of therapy is stressed These are 1 4000 solution of potassium permanganate, 1% aqueous aluminum acetate, half strength Whitfield's ointment The following directions are printed for our patients Because the occurrence of interdigital fissures these lesions may be the portal of entry for staphylococci and eventually cause osteomyelitis

SPECIAL DIRECTIONS TO THE PATIENT
REGARDING CARE OF THE FEET

Many people are affected with itching, scaling, cracking or blisters on the feet especially between the toes This condition is often a ringworm infection or epidermophytosis, as it is called, and is caused

by a vegetable parasite which grows in the skin It is a very common infection and at least 60 per cent of all persons have it at some time It is particularly objectionable in diabetics, because it itches and scratching may give opportunity for other more dangerous infections to get started The disease is usually picked up by walking barefoot on the floors of common shower baths, dressing and locker rooms, infected bath mats or any floor or floor covering where others have walked in their bare feet

The disease most commonly shows itself as a slight cracking or scaling giving the appearance of dead, white skin between the fourth and fifth toes The so called soft corn is one form of this infection In more severe cases groups of small deep blisters come on the soles of the feet and the palms of the hands This form usually itches intensely Most cases are worse during hot weather or when wearing shoes and stockings which heat the feet

Here are some rules for the care of the feet if you have the disease or if you would prevent catching it

1 Wash the feet with soap and water daily
2 Dry the feet with a paper towel or with a towel which will not be used on the rest of the body
3 Stand on a clean bath mat, a newspaper or paper towel when you get out of the bath
4 Never walk on any floors barefoot
5 Do not wear wool stockings next to the skin,—wear thin socks inside which can be boiled
6 Do not wear shoes which heat the feet
7 Use this dusting powder on your feet, in your shoes and in your bath slippers

B	Salicylic acid	2
	Benzoic acid	2
	Talc	100
	Mix	

8 If you have signs of the disease rub a little of this ointment every day on the affected parts

B	Salicylic acid	2
	Precipitated sulphur	2
	Vaseline	30
	Mix	

9 Wash your hands after touching your feet.
10 *Don't scratch if your feet itch,*—put on some ointment
11 If the feet get worse in spite of your treatment consult your doctor about it

For warts, especially the plantar variety, blunt dissection is preferred For corns, no plasters but the use of an emery board, and for calluses, the emery board or better still regular visits to the chiropodist Electrolysis and shaving may be used in the management of hirsutism

Dermatitis Gangrenosa

Following diabetic coma gangrene of the skin of the trunk and arms may occur Sites of hypodermic injection may be the source Thrombotic and embolic phenomena occur in coma and may favor the development of these lesions

Dupuytren's contracture of the palmar or plantar fascia seem to occur more commonly in diabetics even in the younger age groups

Diabetes Producing Lesions

One disorder with skin manifestations has a possible etiological relationship with diabetes, namely, hemochromatosis This is an inborn error of iron metabolism in which it is believed that the production of iron is normal, but that the rate of utilization is slow This is far more common in the male than in the female Lesions in the pancreas, skin, kidneys, lymph nodes and heart are characteristic The bronzing in the skin is due to the presence of iron and melanin

Other skin manifestations of hemochromatosis include the loss of facial, axillary and pubic hair The diagnosis of this condition is made by determination of blood iron, bone marrow iron, liver biopsy, the demonstration of iron in the urine, histological section of the skin for iron or the Fishback test which consists of the injection of potassium ferrocyanide and dilute hydrochloric acid The prognosis for these patients is poor They can be refractory to insulin,

can be *typical diabetics or extraordinarily mild diabetics* and the best form of therapy appears to be phlebotomy

Skin Diabetes

Skin diabetes was described by Urbach and is characterized by a form of pruritus furunculous, sweat gland abscesses, and eczema The sugar content of the skin is high, but hyperglycemia and glycosuria are not present Dietary regulation, alone or with the administration of insulin, may be helpful in this condition

CHAPTER XII

DIABETIC NEUROPATHY

Diabetic neuropathy is a common, distressing and therapeutically unsatisfactory complication of diabetes which has been uncontrolled Although the most common manifestation includes the peripheral nerves, the neuropathy may involve any portion of the nervous system, motor and sensory neurons, spinal nerves, automatic pathways

Classification

Classification of neuropathy is helpful both in understanding the problem, in organizing therapy and in giving an accurate prognosis Karnosh has divided neuropathies into three classes Primary diabetic, diabetic vascular and autonomic dysfunctions

Under primary diabetic neuropathies he includes

1 Primary diabetic neuropathy of the extremities (acroneuropathy)
2 Diabetic radiculopathy
3 Diabetic pseudotabes involving the bladder and joints, especially those of the foot

Diabetic vascular disorders include

1 Ischemic neuropathy
2 Diabetic ischemic disease of the central nervous system

Autonomic dysfunctions include

1 Loss of motor control
2 Sweating deficiencies producing shiny atrophic skin

3 Orthostatic hypotension and tachycardia
4 Argyll-Robertson pupil
5 Gastrointestinal dysfunctions
   a Intermittent nocturnal diarrhea
   b Constipation
6 Sexual impotence
7 Diabetic edema

Etiology of Diabetic Neuritis

Diabetic neuropathy follows periods of uncontrolled diabetes Since nerve tissue is largely dependent upon glucose and cannot derive energy from ketone bodies or fatty acids, insulin insufficiency may be considered one of the most important causes Uncontrolled diabetes would disturb glucose utilization Arteriosclerosis is certainly incriminated in some cases The rôle of vitamins is unsettled and no clinical improvement appears to follow vitamin therapy alone without good diabetic control

Pathology

Little is known about the pathology of diabetic neuropathy The opportunity to study the lesion is rare Griggs and Olsen described three types of cord involvement—degeneration of motor cells of the brain stem and cord, degeneration of the intramedullary portion of the dorsal root fibers with secondary system degeneration producing a tabes like lesion, and pannicula necrosis of the posterior columns occurring especially in the cervical and upper dorsal segments of the cord Atherosclerosis of the nerves and demyelinization of the peripheral nerves has been reported and in many cases advanced general arteriosclerosis has occurred Chemical analyses of the nerves of diabetic patients compared with those of non diabetics showed lower phospholipid, cholesterol and cerebro side content in the diabetic group

Diagnosis

Although the physical examination usually suggests the diagnosis spinal fluid may give the necessary confirmation the most characteristic finding being the excess of protein above the level of 40-60 mg Levels may reach 100-200 mg or more There are no cells The colloidal gold curve shows an elevation to the left in half the cases and a mid zone rise in occasional cases The serology, Hinton test, etc, are of course negative The pressure and fluid dynamics are normal

Acroneuropathy

Symptoms and Signs The most outstanding symptom of diabetic neuritis is pain which is nocturnal in its character The pain may be superficial or deep aching grinding darting or lancing and usually interferes with sleep Paresthesias occur frequently in an incidence as high as 70 per cent Burning sensations are particularly common with numbness tingling chilliness of the extremities and a sensation as if the patient were walking on wool Hyperesthesia may be so marked that bedclothes and clothing may be unbearable Because of the discomfort and length of the attack depression and instability are prominent

The neurological signs include absent or diminished tendon reflexes, the Achilles being absent in 80 per cent patellar reflexes in more than half, biceps and triceps in one third muscle tenderness is common, decreased skin sensitivity occurs in one-half the patients and vibratory sense is diminished in half Mirsky has pointed out that the diminution of the vibratory sense of all diabetic patients is comparable to that of an age two decades greater than that of the patient Paralyses occur frequently Foot drop is the most common wrist drop less common Postural hypotension and tachycardia leading to faintness occur frequently

Cranial Nerves Involvement

Involvement of the facial nerve, *involvement of the fifth*, sixth, eighth, ninth and tenth cranial nerves occur and it has been thought that the frequent attacks of vertigo in diabetic patients might be explained as a neuro labyrinthitis

Pupillary Reactions

Abnormal pupillary reactions are common and confusing. The incidence may be nearly 20 per cent of all patients with neuropathy. The true Argyll-Robertson pupil is observed occasionally. Sluggish responses to light are frequent.

Cord Bladder

The cord bladder has been one of the most distressing complications. The residual urine often measures 500 to 1000 cc. and the bladder is palpable as a pelvic tumor.

Diabetic Diarrhea

Diabetic constipation, diarrhea and gastric neuropathies are most distressing but favorable from the point of view of eventual prognosis with complete recovery. *These cases* often exhibit alarming alternating diarrhea and severe con*stipation. Although the diarrhea occurs* also in the daytime and often appears to be intermittent, the nocturnal character is so common and so distressing that nocturnal incontinence of feces occurs in three-quarters of the cases. The X-ray examination of the colon is normal except for increased spasticity. Proctoscopic examination shows normal mucosa. Many of these patients have achlorhydria even after histamine.

Charcot Joint

The earliest change detected in the foot is thickening of the tarsal region which tends *to progress slowly*, even-

tually to become a thickened deformed foot with a tendency to everge in external rotation with flattening of the longitudinal arch X-ray reveals changes similar to those of the true Charcot joints of syphilis, except that the destruction is usually limited to the tarsal and proximal ends of the metatarsal bones Shields Warren has studied one such foot and found numerous spicules of bone scattered throughout the area of involvement undergoing various stages of absorption with an attempt being made by the remaining periosteum to form new bone

Treatment

Treatment of diabetic neuropathy consists primarily of bringing about good diabetic control and adequate calories with a diet relatively high in good quality protein Polyvitamins may be employed, supplemented with vitamin B complex, vitamin C or B-12 The pain may be relieved by salicylates, warm compresses, baths or heated blankets Sedation in the form of chloral hydrate is essential but opiates, because of the duration of the attack, should be avoided BAL did not yield good results in our hands nor did novocain, ether, or alcohol administered intravenously Special therapy such as pregnant mammalian liver extract advocated by Collins, Kahn, Zelinsky, Greenwald and Stearn has not proved of value in our patients' and although B 12 orally and parenterally combined with insulin has been employed in doses from 30 to 1000 micrograms daily, the results have not been dramatic Paralyses should be handled with appropriate orthopedic and physiotherapeutic procedures

Crude liver extract daily for two weeks, weekly for two weeks and monthly has proved helpful in the management of diabetic diarrheas The total therapy consists of good diabetic control, chemotherapy such as sulfasuxidine or sulfaguanidine, hydrochloric acid if achlorhydria is demonstrated, vitamins and during the acute bouts, costive

drugs such as paregoric and bismuth Change in diet affects the state little but a relatively low residue non irritating diet is to be recommended Over 90 per cent of the cases receiving crude liver extract showed definite benefit

Bladder paralyses have improved with transurethral resections of the bladder neck

Although several patients with Charcot joints have been reported improved with sympathectomy orthopedic applicances to relieve weight bearing have been most helpful in our patients Bilateral leucotomy was necessary for relief of pain in one of our juvenile patients

A good prognosis for recovery from peripheral neuritis and from the diabetic diarrheas may be given

The sequelae of neuropathy include burns cuts and ulcers The combination with retinopathy and nephropathy add *to the importance of this complication* the best management of which remains prevention through physiological control of diabetes

CHAPTER XIII

TREATMENT OF EYE DISORDERS

Eye Complications

The diabetic is susceptible to many visual and eye complications These include

1 Transitory Refractory Changes or Insulin Presbyopia
2 Xanthoma Palpebrarum
3 Argyll Robertson Pupil
4 Muscular Paralyses (most commonly involving the external rectus)
5 Cataracts
    a Congenital
    b Complicata
    c Flocculi
6 Vitreous Opacities and Hemorrhages
7 Lipemia Retinalis
8 Retinopathy
    a Dilatation of the vein
    b Microaneurysms
    c Waxy Exudate
    d Nerve Fibre Hemorrhages
    e Cotton wool Exudate
    f New Blood Vessel Formation
    g Scars of Retinitis Proliferans
    h Hemorrhagic Glaucoma
    i Separation of the Retina

Transitory refractory changes resulting in the loss of the patient's ability to read headlines of a newspaper were ob-

served occasionally even in the pre-insulin era when rapid desugarization with starvation treatment occurred It is not uncommon following the treatment of severe bouts of keto-acidosis or following the early regulation of therapy in the short-term case In fact, 50 per cent of newly treated cases of diabetes show this complication The explanation for this change may be the retention of sodium in the lens, or perhaps it is due to changes in the glucose content of the vitreous A good prognosis for recovery may be given and the patients must be advised to postpone refraction for new glasses for a period of some four weeks after stabilization of diabetes has taken place

Xanthoma palpebrarum occurs with somewhat greater frequency in the diabetic than in the general population The histology and chemistry of this lesion is described in the chapter on skin lesions, page 153 The significance of the lesion is cosmetic only, and the therapy, if disfiguring, is surgical removal

Argyll-Robertson pupils occur alone or with other manifestations of diabetic neuropathy No special therapy is available In like manner, paralysis of the ocular muscles complicates diabetes and again is usually part of the picture of diabetic neuropathy The external rectus is most frequently involved The methods which are used in the general management of neuropathy (see page 163) may be employed in these patients, but time is the most important healing factor

Congenital cataract is part of the general picture of congenital anomalies in diabetes Congenital anomalies occur with somewhat greater frequency in the diabetic than in the general population Extraction is applicable to these patients as it is in the non diabetic population

Lens opacities, wheels and spokes occur at an earlier age in diabetics, although cataracta complicata occurs no more frequently in diabetics than it does in the non diabetic population When these lesions interfere with vision, extrac-

tion is indicated The diabetic withstands this surgical procedure as well as other surgical procedures Because of the greater susceptibility to infections, careful eye cultures are advocated Chemically, the diabetic cataract is characterized by its low phosphorus content and consequent high calcium phosphorus ratio

The juvenile patient, in contrast to the adult, shows a specific lens lesion in the form of flocculi Unlike degenerative complications, this frequently occurs at the onset of diabetes and may be demonstrated upon the first physical examination Such children have usually had a history of symptoms of active diabetes over a period of months or even up to a year without diagnosis and treatment, and often show signs of vitamin B deficiency As the flocculi progress and interfere with vision, discision types of surgery are employed

Vitreous opacities occur in the diabetic as in the general population, but because of the patient's knowledge of retinopathies, they may produce a psychologically disturbing problem

The most innocent lesion found in the retina, because it is completely reversible, is lipemia retinalis It occurs when the blood fat is elevated to the degree that the drawn sample of blood has a creamy appearance It is an occasional complication of diabetic ketoacidosis and disappears within 24 or 48 hours after adequate diabetic therapy has been established

Diabetic retinopathy has become one of the most serious of the complications of this disease It is seen in its most malignant form in those patients whose diabetes has started in childhood, adolescence or early adult life The lesions in these young patients are observed rarely under the tenth year of the duration of diabetes, and are often the first of the vascular lesions to be detected The first change is the dilatation of the vein The caliber of the vein increases gradually to several times that of the artery, and ev

albuminuria and other evidences of diabetic nephropathy Primary malignant hypertension, developing in young diabetic patients, is extraordinarily rare, but indeed papilledema in diabetic patients in the late stage of diabetic nephropathy is quite uncommon In the differential diagnosis, when searching for the cause of hypertension, the following conditions may be considered

(1) *Diabetic nephropathy* The syndrome of diabetes mellitus, albuminuria, and hypertension associated with intracapillary glomerulosclerosis, first described by Kimmelstiel and Wilson, is seen in mild diabetic patients in late life but much more frequently among the severe diabetic patients whose diabetes has had its onset in childhood or in early adult life Pathologic changes include masses of hyaline material found in the glomerular tufts, but in addition usually evidences of pyelonephritis and particularly important are the marked hyaline changes in the arterioles The presence of albuminuria hypertension retinal hemorrhages and frequently an increase in serum cholesterol are important findings Also, the demonstration of birefringent lipid material in the form of small Maltese crosses under polarized light may help Repeated examinations of the urinary sediment are important since hematuria is not a feature of the diabetic nephropathy but rather points toward glomerulonephritis

(2) *Unilateral kidney infection* Occasional cases of kidney infection on one side with hypertension have been relieved by removal of the offending kidney However, in diabetes pyelonephritis is most usually bilateral

(3) *Pheochromocytoma* This tumor of chromaffin tissue, usually found arising in the adrenal but sometimes occurring in other areas may give rise to severe hypertension particularly to periods of hypertensive crisis The importance of recognizing this condition lies in the fact that a number of patients have now been operated upon with removal of the tumor and complete cure of hyperglycemia and glycosuria At the Deaconess Hospital within the last two years, five such cases have occurred The most recent, a

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general dietary treatment, the management of the body weight and good hygiene based upon good diabetic control are the essentials of the treatment. The restriction of salt in

the diet has been employed for the treatment of hyperten sion, especially in the presence of cardiac or renal failure with edema The rice fruit diet has been used in a good many diabetic patients Rigid adherence to a diet containing about 450 grams of carbohydrate, 22 grams of vegetable protein, 3 grams of vegetable fat and about 2000 calories with 20 mg of sodium per day and supplementary vitamins has been employed with a number of diabetic patients at the New England Deaconess Hospital when edema, head ache and retinal lesions were indications After a few weeks this diet has usually had to be liberalized by the addition of some vegetables in place of some rice, small amount of meat or fish

Heart Disease

The frequency of both coronary disease and diabetic gangrene increases with each decade of the duration of the disease and is more than twice as frequent among diabetics with hypertension as among patients with normal blood pressure In contrast to coronary disease other heart lesions are relatively uncommon Congenital heart lesions have oc curred in the babies of diabetic mothers Rheumatic heart disease with auricular fibrillation or with mitral stenosis or regurgitation occurs probably with about the same fre quency among diabetic patients as among non diabetic pa tients Surgical treatment of the relief of mitral stenosis has been accomplished with striking success in a few of o diabetic patients

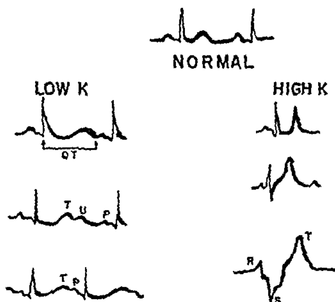
The heart muscle in diabetes shows some differences compared with normal heart muscle Glycogen is prese in considerable amounts, but it is relatively fixed and utilized only in extreme anoxia or after the action of ep nephrine The diabetic heart muscle shows an increase glycogen content and starvation makes little change cardiac glycogen In recent years the disturbances of pota sium and sodium metabolism upon cardiac function, esp

cially during diabetic coma, shock, uremia or lower nephron nephrosis, have been of increasing importance

Low concentrations of potassium in the blood serum are not always closely correlated with depletion of potassium in the intracellular space, so that in patients who have been depleted by reasonable long standing ketosis or poorly controlled diabetes serious cardiac failure may occur even without a strikingly low serum value Therefore, the electrocardiogram may sometimes be a more valuable guide However, when low concentrations of serum potassium are observed or when serum potassium depletion has been present, the following events have been observed (1) weakness of the skeletal muscles, (2) dyspnea, with a shallow gasping type of respiration (3) cyanosis, (4) abdominal distention, (5) nausea and vomiting (6) cardiac enlargement (7) increased pulse pressure, (8) elevated venous pressure and cardiac failure The changes in the electrocardiogram often accompanying the low concentration of potassium or potassium depletion include (1) a slightly prolonged Q T interval, (2) decreased height and inversion of the T wave, (3) rounded and prolonged T waves, (4) depression of the ST segment, (5) prolonged PR intervals with inversion of T waves and extra systoles It is difficult to predict how often and under what circumstances low concentrations of potas sium may be accompanied by anatomic lesions in the heart or when serious symptoms will develop Therefore, frequent electrocardiographic tracings must be used The use of the flame photometer makes possible rapid estimation of the blood values

The disturbances which accompany hyperkalemia are of equal importance and are chiefly to be feared in patients who have diabetic nephropathy and in whom retention of potassium may lead to high values In such patients the signs and symptoms include listlessness, mental confusion, numbness and tingling in the extremities, cold, pallor, slow heart, peripheral vascular collapse and finally cardiac arrest.

Electrocardiographic changes correspond roughly to the gree of elevation of the serum potassium At concentrati of 6 5 to 7 8 millimols of potassium per liter alterations the T waves begin to appear and are constantly pres when the level is above 8 millimols per liter Changes pearing in sequence are (1) the appearance of peal



T waves, (2) increased duration of acute QRS comple (3) increased duration of PR interval, (4) biphasic curve (5) total arrhythmia The danger of potassium poisonin lies in its production of fatal ventricular fibrillation Espe cially in patients who have had diabetic ketosis and also i patients with long standing uncontrolled diabetes, electro cardiograms should be reviewed frequently for evidence o potassium depletion or retention

Treatment of Angina Pectoris and Coronary Arteriosclerosis

The frequency of angina pectoris and coronary arteriosclerosis and diabetes in middle late life increases with duration and with poor control of the diabetes While it is certainly true that there are many patients in middle late life with arteriosclerosis independent of diabetes, the development of diabetes in such patients seems to accentuate its development and to make the prognosis of angina pectoris and particularly of coronary occlusion much more serious than in non diabetics Most observers have found the mortality of acute myocardial infarction in elderly diabetic patients of long duration to be much higher than in non diabetic patients Furthermore, if diabetic ketosis is present at the time of acute myocardial infarction the mortality rate is roughly twice as great as in myocardial infarction in non diabetic patients of similar severity Treatment in patients with early coronary arteriosclerosis for failure or infarction should emphasize reduction of excessive body weight to normal or 10 per cent below normal, the use of diets low in cholesterol and lipids, the control of diabetes by the early use and cautious prescription of insulin, and the reduction of tobacco smoking (preferably its omission)

Coronary occlusion may be regarded as a sign of underlying or potential diabetes in many patients Patients who show glycosuria with or without an elevation of blood sugar during coronary occlusion if followed up within one or two years, thereafter, have been shown in certain series to be really diabetic as indicated by hyperglycemia and glycosuria either with a glucose tolerance test or after a full meal The objective in treating chronic cardiovascular conditions is to restore disturbed physiologic processes to as nearly normal as possible

A Hyperglycemia and glycosuria should be controlled by adjustment of diet and insulin carried out more carefully than in patients without such complications Gradual rather

than rapid *reduction of hyperglycemia* protect against hypo glycemia and the possibility that hypoglycemia will induce angina pectoris The danger of *inducing coronary occlusion* by the use of insulin has been greatly exaggerated Indeed, it can hardly be said that any clear proof exists that myo cardial occlusion either in the presence of coronary arterio-sclerosis or without it is actually or has been actually pro duced by the use of insulin When, therefore, a diabetic patient has uncontrolled diabetes that condition is to be regarded as a load or a burden which should be removed by the proper use of insulin and diet

B Weight reduction aids in controlling diabetes but also tends to prevent progression in the degenerative changes in the arterial system A diet of 150-180 grams of carbo hydrate with 75-100 grams of protein and fat 50-80 grams *is a fair sample of a diet which could be used in a patient* with 150-200 pounds in weight

C Hypercholesteremia and lipemia may play an impor-tant part in the progression of coronary arteriosclerosis both in diabetics and non diabetics Its control should be obtained by a relatively high proportion of carbohydrate in the diet [illegible] content of [illegible]

physicians and actually followed by patients [illegible] ciently restrict the fat part of the diet to have any very definite effect upon blood levels of cholesterol

Acute coronary occlusion has been treated at the Deacon ess Hospital as follows

(1) Complete rest in bed—patients being in bed are not allowed to bathe or turn without help In the severe patients in whom shock and dyspnea are *present*, oxygen has been employed not merely in the pres-ence of cyanosis, but in *others with shock or with* very rapid pulse rates

(2) *Soft or liquid diet* in five small feedings The diet during the course of myocardial infarction should

always be planned to provide calories less than 20-25 calories per kilogram of body weight in the attempt to keep the total metabolism at a level sufficiently low so as to minimize the burden upon the heart

(3) Catharsis with caution during the first phase when shock may be present

(4) Morphine sulphate as needed

(5) Heparin—50 mg intravenously at the same time that the use of dicumarol frequently is begun Dicumarol has been continued with daily determination of the prothrombin time aiming to maintain the prothrombin time which is determined daily between 8 and 15 per cent normal activity Electrocardiograms and sedimentation rates are done daily or at intervals dictated by the patient's need The use of heparin and dicumarol has not been routine, but has been employed roughly in 50 per cent of our patients Patients usually selected for dicumarol treatment have been patients with severe occlusion accompanied by shock, fever, leukocytosis, rapid pulse rate, and cyanosis Insulin is used if hyperglycemia, glycosuria and especially if any ketosis is present During shock from coronary occlusion, the CO_2 content of the blood, apparently due to shock, does not require treatment

In accidental cases of insulin hypoglycemia there is no evidence of harmful effect upon the heart not already damaged by coronary arteriosclerosis The use of insulin in the patient with coronary occlusion is an essential part of the control of diabetes if the patient is exhibiting marked glycosuria and hyperglycemia

Diabetic Nephropathy

The kidneys of diabetic patients may show any of the processes due to disease or to failure of development which are found in non-diabetics Thus, congenital absence of

double ureters or horse shoe kidneys occur The renal le sions which frequently occur in a diabetic may be listed a follows

(1) Reversible changes include glycogen or fat deposit in the renal tubules
(2) Arteriolarsclerosis (necrosclerosis)
(3) Intercapillary glomerulosclerosis
(4) Acute or chronic pyelonephritis including the necro tizing renal papillitis
(5) Arteriosclerosis

Deposition of glycogen in the renal tubules merely indi cates glycosuria, whereas, fat deposits in the tubules indi cate injury to the tubular epithelium, frequently seen in diabetic coma The last four changes commonly occur to gether especially in young diabetics of long duration It was in 1936 that Kimmelstiel and Wilson pointed out the asso ciation of diabetes, nephrotic edema, gross albuminuria, hypertension and intercapillary glomerulosclerosis This syn drome has assumed increasing importance with the passage of the years It has proven to be associated with other lesions so that at present kidney involvement found in diabetic patients of long duration is almost invariably of mixed morphology It is the combination of arteriolarsclero *sis*, acute and chronic pyelonephritis, intercapillary glo merulosclerosis and arteriosclerosis which is seen with the greatest frequency and which is called diabetic nephrop athy

Diabetic nephropathy may be seen in diabetic patients of any age It was first described as a lesion commonly found in mild diabetes of middle and late life Actually, its inci dence is now known to be much greater in the severe dia betes of youth than in the mild diabetes of later life It is clearly related to the severity of the diabetes and the char acter of its treatment The treatment of the diabetic ne phropathy should begin with prevention Here the essential

thing is the early diagnosis of diabetes and its early control from the very onset Attempts to control diabetes in young patients with diet alone with the result that the use of insulin is postponed for one, two or more years is an invitation to later disaster Failure to prescribe a diet adequate, not only in calories, but in minerals and vitamins and then the failure to make sure by the adequate use of insulin that the diet is normally metabolized lays the foundation for later nephropathy The actual diagnosis of diabetic nephropathy depends upon the finding of persistent albuminuria As time goes, on retinal lesions typical of the diabetes, mainly the aneurysms, retinal hemorrhages and the typical hard, waxy diabetic exudate may appear In some patients the retinal lesions appear before albuminuria More commonly, albuminuria is followed by a period of months or years in which apparently benign edema is present This period of benign edema is readily controlled by various measures, but may be followed by this stage of nitrogen retention The treatment is summarized on page 186

Vascular nephritis is fairly frequent especially in early stages among elder diabetics Acute glomerulonephritis is relatively uncommon It is readily distinguished from the typical diabetic nephropathy by the hematuria Although a few red cells may be found in the sediment in the patient with diabetic nephropathy, in general the typical hematuria of glomerulonephritis is never seen In the treatment of glomerulonephritis during the stage of edema and hypoproteinemia, in addition to bedrest and moderate restriction of fluid and salt intake, transfusions of human albumin solution have at times been beneficial However, precautions in limiting the frequency and speed of injections are important Even in the young diabetic patients of long duration pulmonary edema develops most unexpectedly following injections of albumin solution or of acacia

CHAPTER XV

DIABETIC NEPHROPATHY

Since the publication of the report by Kimmelstiel and Wilson, much has been written about intercapillary glomerulosclerosis found frequently at postmortem examination In patients with onset of diabetes in childhood dying after a duration of at least 15 years, particularly in those with poor chemical control, characteristic lesions described by those authors are invariably present but accompanied by other lesions in varying degree The combination is so characteristic and so predominant at autopsy in such patients that it is preferable to designate the clinical syndrome as the diabetic nephropathy The histopathological findings characteristic of diabetic nephropathy consist of a combination of lesions including the following intercapillary glomerulosclerosis, acute and chronic pyelonephritis, arteriolosclerosis and arteriosclerosis Evidences of glomerulonephritis are rarely seen The combination of lesions just described, resulting from infections, degenerative or perhaps nutritional or endocrine factors, is not a frequent pathological finding in any disease except diabetes

Pathology

Intercapillary glomerulosclerosis occurs in two forms—nodular and diffuse, the former being especially characteristic of the juvenile type diabetes and consists of the presence of one or more round, ball like hyaline masses in the glomerular tuft and having an intact capillary running over

the surface of the nodule which has given the name intercapillary glomerulosclerosis The hyaline material is now known to contain a mucopolysaccharide It has also been emphasized that such lesions also show characteristic lipid involvement

Symptoms and Signs

The clinical manifestations of this complication are the following It is suspected by the appearance of albuminuria in a quantity of 50 mg or more in the absence of pyuria Sometimes edema precedes the albuminuria The urine contains little in the way of cells or casts, but often contains doubly refractile bodies appearing as a maltese cross structure These have been considered pathognomonic of this condition The specific gravity may be normal or may be elevated because of glycosuria For a long period of time the non protein nitrogen remains normal as does phenolphtalein excretion The urea clearance tends to diminish gradually The cholesterol rises, the serum protein falls and there is a reversal of the A/G ratio and the following electrophorectic pattern Albumin and gamma globulin decrease, alpha$_2$ globulin increases protein bound carbohydrate, alpha$_2$ and beta lipoprotein are increased The blood pressure may be normal for many months or years and gradually rises to hypertensive levels In addition, these patients usually show characteristic diabetic and nephritic retinopathy and also may exhibit calcification of the vessels throughout the body The capillary fragility index is elevated

Course

Usually the disease progresses in clinical stages as follows The first phase is the nephrotic stage followed by one which is characterized by severe anemia The third is a salt losing stage, fourth, uremic, fifth, acidotic; sixth, cardiac; and seventh, encephelopathic

Treatment

Prevention of diabetic nephropathy consists of four parts First, the careful chemical control of diabetes, second, correction of infection, particularly pyelonephritis which often appears to be the initial starting point of the complications third, the avoidance of ketoacidosis, and fourth, the prescription of a diet which is adequate in high value protein, 1½ 2 grams per kilogram of body weight, and finally the selection of fats which are vegetable in origin and most easily metabolized by the body The actual treatment of the condition is symptomatic Thus, in the nephrotic stage the diet should be low in sodium, one gram or less per day, the protein content of the diet, 1-2 grams per kilogram of body weight. The acid ash diet has received a certain amount of favorable attention, but has become less popular than it was formerly It may be obtained as follows milk, fruit and the basic vegetables should be restricted and acid forming foods, meat, eggs, fish, bread and cereals prescribed

The drug therapy which is helpful during the nephrotic stage is ammonium chloride in a dose range of from 4-8 grams prescribed cyclically for three days and omitted for three days, or in similar fashion, Diamox, 250 mg daily for three days, then omitted for three days A combination of ammonium chloride and potassium chloride or nitrate may be desirable Mercuhydrin may be administered in 1-4 cc doses intramuscularly Patients may also be taught the use of Thiomerin which may be administered subcutaneously and Neohydrin for oral administration Xanthines, 2-8 grams daily, are particularly advocated if nausea occurs Salt poor albumin, amigen or acacia may be used under special circumstances or even the exchange resins In the anemic phase, multiple small transfusions, particularly of packed red cells, may be helpful Iron, as ferrous sulphate or copper, may be prescribed During the salt losing stage, salt restriction may be removed and sodium chloride adminis

tered cautiously Large quantities of sodium chloride, however, appear to be trapped by these patients and edema may become progressively worse if this therapy is pushed too aggressively If the patient is eating fairly well, salt may be supplied with the diet If the food intake is low, normal salt solution may be administered until the chloride level *rises in satisfactory fashion*

In the uremic stage, the protein of the diet is moderately restricted, the low sodium diet is continued and the main part of the calories administered in the form of carbohydrate and fat If acidosis develops sodium lactate is administered intravenously in the form of one sixth molar solution, especially when the carbon dioxide content of the blood falls to 15 milliequivalents or below, or if the patient develops hyperpnea If the phosphorus rises then colloidal aluminum hydroxide, 8 cc may be given four times daily and calcium gluconate, 10 cc of a 10 per cent solution if tetany occurs When heart failure develops, bed rest, restriction of fluid and digitalization are indicated, and for the encephalopathy, magnesium sulphate in 2 cc doses of 50 per cent solution intramuscularly as necessary Hypotensive and anticonvulsant drugs may be prescribed and lumbar puncture may be therapeutic

The more radical forms of therapy which have been suggested include the rice diet, artificial kidney, peritoneal or intestinal gavage As this type of nephropathy is chronic and progressive, the two latter play a less important rôle than they do in more acute forms of renal disease Bilateral adrenalectomy has been advocated in those patients with intercapillary glomerulosclerosis where the prognosis appears especially poor More recently, medical adrenalectomy has been attempted with large doses of cortisone and even more recently by use of amphinon A followup of patients with surgical adrenalectomy has, on the whole, been discouraging and prevention is certainly to be recommended rather than such radical forms of therapy Heparin altering the

lipoprotein content of the blood has been recommended by Gofman

Effect of Nephropathy upon Ketoacidosis and Insulin Hypoglycemia

In contrast to some current statements in the literature that the patient with intercapillary glomerulosclerosis has not had ketoacidosis or diabetic coma prior to the development of the nephropathy and does not contract ketoacidosis or diabetic coma during this complication, we find particularly in our younger patients that many attacks of ketoacidosis have characterized their past histories and the development of ketoacidosis as well as renal acidosis has been one of our more serious problems in the management of such cases in the past few years These patients will manifest edema in spite of severe acidosis Therefore, the fluid therapy must be given cautiously As the potassium levels may be found to be very high, a careful evaluation of the electrolyte pattern or electrocardiographic examinations must be done The prognosis for recovery from ketoacidosis in these patients with complicating intercapillary glomerulosclerosis is obviously poorer than is the prognosis for recovery in the average diabetic patient

In addition to susceptibility to ketoacidosis, these patients become progressively susceptible to insulin hypoglycemia so that the insulin requirement may drop to fantastically low levels for periods of time These patients may actually require no insulin whatsoever The explanation for this may be inadequate food intake, poor absorption from the gastrointestinal tract, perhaps because of edema With advancing lesions, adrenal failure is suggested by the fall in excretion of 17 keto and 17 hydroxysteroids

Prognosis

In spite of the seriousness of this complication, pregnancy may occur in young female patients with diabetic nephrop-

athy (See section on Treatment of Diabetic Pregnancies)

The prognosis for the patients with nephropathy is poor Progression, however, is slow The average duration of life after albuminuria was first recognized in fatal cases in our young group was 5 years, but the average duration of life for the living cases in this same group exceeded that of the fatal, for it was 6 years

TABLE 22

TREATMENT OF NEPHROPATHY IN YOUNG DIABETICS OF LONG DURATION

Diabetic nephropathy is commonly first indicated by recurring edema persistent albuminuria and in many cases an increase in the plasma lipids (nephrotic phase) Later manifestations include hyper tension increased albuminuria cylindruria cardiac failure and uremia In occasional patients periods of glomerulonephritis may occur Renal infection is a frequent component in the clinical course Anatomic findings in cases with diabetes of 15 years duration or more include arteriolar nephrosclerosis Kimmelstiel Wilson lesions arteriosclerosis and pyelonephritis

NEPHROTIC STAGE

Clinical

Albuminuria edema normal non protein nitrogen (40 mg per 100 cc or lower) low serum protein, increased serum lipids (cholesterol may be 250 to 1000 mg per 100 cc)

Management

A Diet as indicated for diabetes Protein limited to 1 gm per kg per day Salt limited to 1 gm per day

B Salt substitutes may be used

C. Acid-ash diet (but not at expense of sodium restriction) To obtain an acid-ash diet milk fruit and certain vegetables,

UREMIC STAGE

Clinical

Nitrogen retention (non protein nitrogen 45 mg to 100 mg per 100 cc or higher) Hypertension (usual) albuminuria cylindruria retinopathy and edema variable

Management

A Diet as indicated for diabetes except protein limited to as little as 0.5 gm per kg body weight per day Sodium limited to as little as 0.5 gm. per day when the serum sodium is 150 mEq or higher Liquids may be forced up to a point where gain in weight occurs. Insulin requirement may decline

lipoprotein content of the blood has been recommended by Gofman

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NEPHROTIC STAGE	UREMIC STAGE
Clinical	*Clinical*
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Management	*Management*
A Diet as indicated for dia betes Protein limited to 1 gm per kg per day Salt limited to 1 gm per day B Salt substitutes may be used C Acid ash diet (but not at ex pense of sodium restriction) To obtain an acid ash diet milk fruit and certain vegetables	A Diet as indicated for diabe tes except protein limited to as little as 0 5 gm per kg body weight per day Sodium limited to as little as 0 5 gm per day when the serum sodium is 130 mEq or higher Liquids may be forced up to a point where gain in weight occurs Insulin require- ment may decline

which are basic, must be restricted The acid forming foods include meats eggs fish bread and cereals

D Moderate or severe edema combated with

1 Ammonium chloride 4 gm daily for 3 days followed by *mercurial diuretic*

2 Human salt poor albumin intravenously 25-50 grams per day may be used

3 Digitalis and bed rest if heart failure is present

E Anemia less than 9 grams per cent responds best to packed cell transfusions

F Treatments of doubtful value include thyroid extract *plasma hydrolysate infusions* cation exchange resins adrenal steroids

G ACTH in short courses when nephrotic status stable

H Mercuhydrin, 1 2 cc intramuscularly (occasionally I V) following the ammonium chloride period Thiomerin for subcutaneous use and Neohydrin for oral use Mercury cautiously!

I Cortisone 200 mg as medical adrenalectomy may occasionally be tried

B For nausea chlorpromazine (with caution) Guard against vomiting

C Anemia of less than 9 grams per cent best treated with packed red blood cells

D Severe hypertension may be treated with rauwolfia hydralazine *or veratrum—meanwhile* observing renal function closely

E Cardiac failure requires bed rest, usually small doses of digitalis diuretics according to the degree of congestion (mercurials NH_4Cl Diamox or xanthines)

F Electrolyte abnormalities

1 Potassium excess may be lethal restrict dietary potassium (fruits protein), in crises give *glucose infusion with insulin.*

2 Acidosis hyperpnea treated with ⅙M sodium lactate

3 Tetany relieved by 10 per cent calcium gluconate *I V.*, later P O

4 Artificial kidney may be useful in crises

5 Correction of hypochloremic or hyponatremic states with appropriate electrolyte solutions

G Encephalopathic convulsions treated with barbiturates draining of 30 cc spinal fluid, antihypertensive drugs (*hexamethonium or veratrum*) Magnesium sulphate 2 cc 5 per cent. Solution I M or I V P R N (can use 20% I M)

Renal infection (pyelonephritis) may occur at any stage Chemotherapy under strict medical supervision is indicated according to f the o ganisms

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CHAPTER XVI

MANAGEMENT OF DIABETES WITH SURGICAL COMPLICATIONS

Attitude of Physician

Modern treatment of diabetes which began with the discovery and use of insulin, has nearly eliminated the diabetic patient's fundamental handicaps, namely, the development of acidosis after anesthesia, failure to heal and inability to maintain good nutrition Therefore, no longer is it proper to postpone needed surgery, but rather it becomes the duty of the family practitioner to emphasize to all diabetic patients early in the course of their disease that today diabetic patients can avail themselves of all modern discoveries and advances in surgery If the patient s diabetes is kept under good control with the proper diet he is hardly more serious as a surgical risk than a non diabetic patient of the same age and general condition If all diabetic patients learn early in the course of their treatment that the important thing is the early reporting of symptoms, then early diagnosis will make possible treatment by surgery which will in many cases be preventive as well as curative Actually, today the better preparation for the surgical procedure, the use of parenteral feeding and most of all the use of the new Antibiotics, make the surgical procedure fast and more safe but also make the convalescence less protracted and more secure

All types of surgery can be performed upon diabetic pa tients Actually, in 8,000 operations upon diabetic pa-

tients in the New England Deaconess Hospital one fifth of the patients were under 40 years of age, two fifths between 40 and 60 years of age and the remainder of the group from 60 to 90 years of age

The variety of operations has gradually altered during recent years Roughly, one third of the operations consisted of amputations of the toes or lower limbs Next in frequency were operations for superficial and deep septic processes These two groups make up nearly one half of the total operations Operations upon the thyroid gland, laparotomies tonsillectomies, genito urinary operations and operations for the removal of cataracts, relief of glaucoma and finally operations for pulmonary tuberculosis or pulmonary carci noma form a new group

The prognosis has distinctly improved in all types of surgery The factors which favor success are first the elim ination of elements which formerly caused many *losses* namely, acidosis and a liability to infection Ketoacidosis has become only an accident Danger of clean wounds becoming infected is slight with the diabetes properly con trolled In the presence of infection one must admit that the diabetes may become worse and even acidosis may develop rapidly However, with the new antibiotics, control of infec tions may be assured provided at the same time that the diabetes itself is controlled The chief disadvantage in much diabetic surgery here is the factor of old age with the at tendant arteriosclerosis and the slow healing of old tissues The complications in the cardiovascular system are those chiefly of coronary occlusion, pulmonary embolism and cerebro vascular accident

The factors which favor surgical success are first of all an early diagnosis and an early decision to operate This does not mean that every surgical patient should be operated upon within 48 hours after admission to the hospital Indeed, today much more time is taken in preparing the patient for

operation than formerly Medical treatment is labile and can be adapted to the condition in hand with adequate preparation in the way of fluid administration and sufficient diet Surgery is vastly more safe than ever before The adjustment of the diet to the surgical requirements is important If there is no need for haste, any of the well recognized dietary systems recommended to get the patient free from sugar and acidosis will be successful The time spent, therefore, in bringing the diabetes under good control, in securing adequate hydration and in establishing regular bowel movements is well spent It is the procrastination in the handling of the surgical lesion itself which is often most harmful to the feet where delay in assessing the circulation to the foot and determining the degree of circulatory impairment together with a long continued trust in antibiotics may allow infection and gangrene to proceed to a point *where the opportunity to save the whole foot by the amputation* of one or more toes has been lost More serious is the matter of procrastination in serious abdominal lesions

Among the metabolic considerations in preparing the diabetic for surgery may be mentioned the fact that there is a great advantage in storing carbohydrate in the body and particularly in the liver before operation With an adequate store of carbohydrate the stress of operation and possible nausea and vomiting are much less likely to lead to excessive fat combustion and consequent ketosis

The danger of a clean wound in a diabetic becoming infected is slight, if the diabetes is properly controlled, not merely before operation, but during the post-operative period It is true the infection may well have made the diabetes rapidly worse Under these circumstances not only may infection extend but infected areas may become necrotic and actually gangrenous not merely in the extremities but even within the abdomen However, if infection is prevented or having occurred is brought under control, healing

is today usually reasonably prompt except in diabetic patients in which old age or lack of diabetic control for long periods do contribute to the situation Often, however, in patients in the hospital the presence of unexpected glycosuria during the convalescence may be the first clue to infection as yet undisclosed This may well be true even before the temperature chart or the pulse record shows evidence of the infection The major handicap today in diabetic surgery is the factor of old age and the vascular disease which accompanies either old age or the premature vascular disease seen in much younger patients whose diabetes is of long duration Today this group of patients forms an increasingly large proportion of the surgical population on the diabetic service This primarily is a factor in the healing of wounds and in the induction of lesions of the extremities dependent upon more blood supply However, it also affects the post operative results because the chief cause of death in surgery of the extremities is the group of vascular accidents including coronary occlusion, pulmonary embolism or cerebral hemorrhage or thrombosis

Diet During and After Diabetic Surgery

The dietary treatment must be based upon the study of the patient s present condition and the record of his past treatment The first consideration is the presence of glycosuria, hyperglycemia and ketosis Decisions as to insulin and diet with the type and amount of fluid administration will be primarily concerned with these factors However, in patients long uncontrolled for periods of months or years in addition to loss of weight, dehydration and frequent acidosis, there may also be significant malnutrition with losses in protein and fixed base and disturbances in vitamin metabolism Additional factors such as achlorhydria, diarrhea and the symptoms due to the surgical complication itself may have produced in the patient at the time of his arrival at the hospital, varying degrees of tissue starvation

Diet Before and After Operation

In patients whose preparation for operation is not hurried so that a period of two or three days may be allowed, no special change need be made in the regular diet except the adjustment of insulin and the reduction of the total calories consistent with the resting condition in the hospital Usually for such patients coarse diabetic foods should be reduced in amount or omitted unless the individual situation requires particular food On the morning of operation our usual practice is to give no food within 8 or 10 hours of operation unless the operation is an extremely minor one In minor operations no special administration of glucose solution or pre operative enema may be necessary In major operations, however, usually the patient has pre operative preparation including enema according to the surgeon's direction, and if the patient has been taking doses of insulin from 40 units to 100 units a day he will receive on the way to the operating room roughly two thirds of his usual insulin dose Administration of glucose solution intravenously is not a routine Indeed, in many non emergency operations upon patients in good condition, the administration of glucose solution may well be left until after operation and then given or not according to the needs of the patient However, the fact remains that in many patients, particularly where there is some uncertainty about the action of insulin during and following operation and particularly where it is pretty certain that intravenous fluids will be required after operation, it has become the custom to administer 1000 cc of 5 per cent glucose in normal saline on the morning before operation at the same time that insulin is given

Following operation, if the patient is unable to take food by mouth it becomes necessary to rely upon intravenous fluids and of these, the most commonly employed is intravenous glucose solution in saline In patients in whom salt solution is contra indicated for cardiac or other reasons, 5

per cent glucose solution in water is commonly employed If after 24 hours the patient can begin to take fluid, the simplest foods are the best Thus, oatmeal gruel made with water, hot tea or coffee with crackers or toast may be given freely Ginger ale and orange juice with egg white are commonly used On the second post operative day milk and other cooked cereals and custard may be given Thereafter, the diet is increased according to the patient's desires and surgical requirement In general, it is desirable that every diabetic patient should have 100 150 grams of carbohydrate daily When that amount is not taken by mouth it is usually supplied by parenteral administration of glucose by vein Two and one-half per cent dextrose in physiological salt solution may be used under the skin For special indication such as damage to the liver, as much as 250-300 grams may well be given A diet approximately 160 175 grams of carbohydrate with 75 85 grams of protein and 85-100 grams of fat will be attained within a week or ten days

When the patient is ready for discharge and has been up on his feet for a reasonable period, the diet planned for activity at home will in general provide for 30 35 calories per kilogram with roughly carbohydrate 175 200 grams, protein 90-100 grams and fat 80-115 grams

We rarely attempt by rapid vigorous use of insulin to make patients, particularly those with serious infection, sugar free before operation It is very easy because of the long action of protamine zinc insulin or NPH insulin to overshoot the mark and produce serious hypoglycemia Certainly we do not reduce the diet deliberately in an attempt to make the patient sugar free

The advantage of routine blood sugar determinations in preparing patients for surgery needs emphasis In the first place a good many patients who are supposed to be mild diabetic patients will be found after surgery or before, to show a very conspicuous rise, and which may, when following

surgery under the stress of anesthesia and the operation itself, lead to serious diabetic acidosis In surgical patients who have serious diabetic ketosis, emergency treatment of acidosis is indicated In those patients where the urgency of the surgical situation, as in acute appendicitis, require immediate surgery then the closest followup of the patient's blood sugar, urine test and evidences of ketosis will be indicated

In emergency situations such as acute appendicitis, where operation must be performed as soon as possible or at best within 24 hours, it is rarely wise to make great changes in diet or in the treatment of the patient in the attempt to make the urine sugar free or to reduce hyperglycemia to a normal level In such cases, the use of repeated doses of insulin with a blood sugar determination every two or three hours will bring about a decline in the blood sugar level so that the physician can feel that he knows the sensitivity of the patient to insulin and that the control of the carbohydrate metabolism, as indicated by the blood sugar level, is within his power Thus, if a patient is admitted with a blood sugar of 500 mg and with moderate doses of insulin given every two hours, at the end of eight hours the blood sugar has been reduced to 250 mg then it is evident that if the patient has required 50 or 75 units for this effect he is not resistant to insulin and that following surgery he may not be expected to require insulin in amounts of 100 200 or 300 units The development of insulin resistance may take place under the influence of infection anesthesia and surgical shock and will, of course, require much larger doses of insulin However, such is a rare occurrence and the existence of insulin resistance before operation will probably have been disclosed by the behavior of the blood sugar level when insulin is given fairly rapidly in the preceding 12 hours Thus, in a patient with blood sugar of 600 or 700 mg upon admission, if the administration of 100-200 units

failed to reduce the blood sugar level, he is evidently in a state of relative insulin resistance It may, therefore, be expected that following operation insulin must be administered in doses of 50 100 units at a time and the effect upon blood sugar level watched at intervals of 2-4 hours In certain cases with serious insulin resistance at the time of surgical operation, the use of a much more concentrated insulin preparation is often necessary such as the U 500 preparation Sometimes the administration of insulin intravenously is necessary to be assured of rapid action

In all operations it is important to avoid the risk of producing hypoglycemia Thus, in one child with a simple tonsillectomy hypoglycemia of severe character occurred while the patient was still under ether and no symptoms were recognized On return to the ward the patient's blood sugar was found to be at a critically low level and treatment fortunately was instituted before any serious damage resulted The possibility of inducing hypoglycemia therefore, when patients with diabetes are operated upon as emergency cases must always be borne in mind in deciding for or against doses of insulin of moderate or unusual size

Insulin at the Time of Surgery

In general, the use of insulin is indicated in the great majority of operations carried out upon diabetic patients except in the mildest cases It should not be forgotten that *the effect of anesthesia and especially of ether may result in* an apparently mild diabetes becoming acutely severe with ketosis during the hours which follow surgery It is this fact, which makes pre operative precautions imperative All patients, especially those over 35 years of age, admitted for operation under general anesthesia should have a blood sugar determination one hour after breakfast and at the same time a test for glycosuria unless they are already

known to be diabetic If this procedure were followed instead of testing the fasting blood sugar and urine, many true diabetics would be discovered and the hazards of surgery would be reduced for that group In such patients discovered with diabetes without symptoms, the amount of insulin required might be very small but the efficiency of 5, 10, or 15 units of insulin in early patients with diabetes of relatively short duration is so much greater than in patients with diabetes of long duration and chronically uncontrolled, that the value of even small doses of insulin has not been sufficiently appreciated

If insulin has been used regularly by the patient, in general the same total number of units in the 24 hours at the time of operation may be given, but usually it is evident that one should divide the total dosage into smaller and more frequent doses Thus, on the morning of operation perhaps one half to two thirds of the usual dose of protamine zinc insulin or NPH insulin may be given before the patient goes to the operating room Then, following operation, based on tests of the urine and blood every 2-4 hours, supplementary doses of regular insulin may be given in the attempt to control hyperglycemia and glycosuria Administration of small doses of insulin every 3-4 hours, or more rarely, every 6-8 hours will control hyperglycemia with little danger of hypoglycemia Many physicians prefer to depend upon the use of regular acting insulin in place of protamine zinc insulin feeling that shorter duration of action of the regular insulin enables the physician to change his tactics if hypoglycemia develops Blood sugar tests late in the forenoon and the middle of the afternoon may be sufficient in some cases without recourse to the regular testing every 3-4 hours

In the patient who has not had insulin previously, it may well be used if two successive urine specimens contain sugar or especially if blood sugar values are repeatedly above normal

Resistance to insulin does occur at times of infection or

when there is allergy to insulin or in obese patients and often in patients with hypertensive disease In them, larger doses of insulin will necessarily be employed However, the danger of insulin reactions is always in the mind of both surgeon and physician during and following surgery Patients with mild diabetes who receive glucose solution following surgery may develop serious hypoglycemic reactions 3 to 5 hours later Although the blood sugar immediately rises at 60 minutes after glucose, there may be stimulation of the pancreas from the high blood sugar and in such patients hypoglycemia may result 3 to 5 hours later especially if any insulin has been given Therefore, it is our usual rule not to give insulin on the strength of a positive urine test within 2 hours after glucose solution, but to wait for another test after the bladder has been once evacuated During the last few years, protamine zinc insulin has become increasingly frequently used in diabetic patients At present the newer modifications including NPH insulin and Lente insulin are being substituted During one period at the Deaconess Hospital among 385 patients, 132 were admitted taking a single dose averaging 22 units of protamine zinc insulin, whereas, at discharge the same patients were taking protamine insulin averaging 24 units per day In the same group of 385 patients 152 patients were using both regular and protamine zinc insulin requiring an average of 50 units total upon admission At discharge, 162 patients took an average of 12 units of regular and 45 units of protamine zinc insulin NPH insulin was then being used by 62 patients, but in the next few years it is quite likely that distribution of insulins and the dosages will be modified again

Anesthesia in Diabetic Surgery

The choice of an anesthetic agent and especially its method of administration are important factors in the outcome of surgical operations for diabetic patients today Almost any type of anesthesia can be used, thanks to the use of insulin

However, it must not be forgotten that general anesthetics have specific effects and that often these effects are magnified in the diabetic patient of long duration and particularly the diabetic patient who has been under poor control for periods of weeks or months before surgery Whether it be depleted storage of carbohydrate in liver and muscle or depletion of mineral reserve or disturbances in vitamin and hormone relationship, the fact is that such patients, often presenting anemia, hypoproteinemia in addition to disturbances in blood sugar level, may offer a serious problem to anesthetists

The first point to be remembered is that diabetic patients of the type just mentioned are not good subjects for pre operative sedation of the same degree as non diabetics A working rule at the Deaconess Hospital was that not more than half the usual pre operative medication should be given to a diabetic patient before major surgery In the obstetrical diabetic patients no pre-operative medication is given The avoidance of apprehension on the part of the patient is important, but it is true that many diabetic patients prefer to go to the operating room without preliminary medication Obviously the reverse is true in certain patients who are extremely fearful of the operating room Every effort should be made to shorten the period of anesthesia no matter what type of anesthetic is used The avoidance of anoxia during anesthesia is a prime consideration in all patients, but is particularly important in the diabetic patient who, particularly after the age of 50 years, may well have, thanks to the patched distribution of his generalized arteriosclerosis, areas extremely vulnerable to anoxia either in the brain, in the heart, the kidneys or the legs Morphine and barbiturates, as pre-operative medication, tend to produce anoxia When used in addition to nitrous oxide anesthesia dangerous anoxia may result In general, the choice of anesthetics should be first, local anesthesia, second, spinal anesthesia, and third, general anesthesia

Local anesthesia should not be accompanied by the use of tourniquets, particularly on fingers or the extremities The danger of necrosis is thus intensified

In amputations of infected toes or legs spinal anesthesia has been by far the safest in the experience obtained during the last 25 years at the New England Deaconess Hospital While some accidents have been reported no really serious complication has occurred during the last 15 years Such incidents as headache, persisting pain in the leg, extra ocular paralyses have been so rare that it is difficult to recall more than five The arachnoiditis and paralyses following anesthesia which have been described elsewhere have not been seen in our experience It is true, however that spinal anesthesia has rarely been employed in young patients General anesthesia under pentothal has been most helpful to some patients where because of cardiac or pulmonary conditions inhalation anesthesia seemed contraindicated Ether and cyclopropane have been frequently used Often gas-oxygen induction has preceded etherization

Gangrene and Infections of the Extremities

Incidence Gangrene, dependent upon the diabetic predisposition to arteriosclerosis obliterans and infection, has been a frequent and dreaded complication in older diabetic patients, but today presents a problem even among much younger diabetic patients because of their much greater duration of the disease A third factor has affected the total lesions in the diabetic feet in recent years as the number of patients with diabetes of long duration has increased This factor is the diabetic neuropathy, characterized by loss of sensation, comparative freedom from pain with extensive lesions, degeneration in bones and joints of the Charcot type and usually with extreme susceptibility to infection and relatively slight trauma In the study of any lesions in diabetic feet and in the prophylactic care of diabetic feet, therefore,

the physician must have constantly in mind first, the presence or absence of impaired blood supply due to arteriosclerosis obliterans, second, type and severity of infection present, and third, the presence or absence of the diabetic neuropathy

The frequency of diabetic foot lesions will vary with the standards employed in determining their presence Thus, if one measures the presence or absence of neuropathy in diabetic feet by means of the presence or absence of the ability to recognize normally tuning fork vibration, then some degree will be found in from 80-100 per cent of diabetic patients with a duration of more than five years who are over 30 years of age, the percentage increasing with each decade of age If one includes all cases of epidermophytosis as well as infections of corns and calluses then, too, mild infections, capable of rapid change into a more severe form will be found in a considerable percentage of all diabetic patients if one follows them for more than a few years Finally, varying degrees of arteriosclerosis obliterans will be found from the age of 30 years onward depending upon the duration of the diabetes and the character of its control On the other hand, if only lesions are considered which have caused hospital admission, experience in various clinics will vary As a cause of death gangrene has fallen, in the experience of the Joslin Clinic, to only one per cent of total deaths This change is due to the improvement in medical diagnosis, the care of the diabetes and particularly to improved surgical technique It does not take into account the tremendous morbidity from diabetic foot lesions Thus, in one twelve month period in six hospitals in the city of Boston 502 patients were admitted to the wards for diabetic foot lesions Of these 32 died in the hospital sometime following surgery, sometimes due to coronary occlusion or other vascular accident Fifty per cent of this group had serious occlusive vascular disease in the extremities, so although they may have left the hospital

on this admission their future admission is certain to occur *unless death occurs from some other cause* Every diabetic patient, therefore, past the age of 30 years as the duration of his diabetes increases should be examined with particular reference to these three factors in the initiation of diabetic foot lesions

Age is an important factor in the development of serious foot lesions and particularly gangrene Thus, among patients with diabetes having its onset after the age of 70 years probably 10 per cent will have serious foot lesions In addition to age, however, other factors are of importance *namely, arteriosclerosis, infections and the neuropathies* Gangrene occurs chiefly in obese patients with diabetes of long standing and low insulin requirement It often results from very slight accidents or traumata which have been too long neglected Epidermophytosis has become a predisposing *cause permitting more serious and malignant infections* to enter the weakened skin The susceptibility of the diabetic tissue to necrosis from slight pressure, from changes in temperature, from infections is an outstanding feature In the remarkable postmortem records of E T Bell including *28 240 males and 15,119 females over 10 years* of age, arteriosclerotic gangrene occurred in 0 66 per cent of non diabetic males but in 24 9 per cent of the non diabetic females but in 23 8 per cent of 499 diabetic females Thus, Bell concluded that gangrene due to atherosclerosis or arteriosclerosis *develops nearly 40 times as frequently* in diabetics as in non diabetics

Occlusive Vascular Disease (Arteriosclerosis Obliterans)

Diabetic patients develop this pathologic change in the arteries, particularly of the legs, at an earlier age and at a more rapid rate than non diabetics The basic lesion from the standpoint of pathology is atherosclerosis or a combination of *atherosclerosis* and *medial arteriosclerosis* The lesions may first be seen in the distal portion of the femoral

artery, but actually in young diabetic patients the first calcareous deposits seen by X ray are usually in the lower leg. Later, calcification appears at higher levels such as the femoral arteries, pelvic arteries and finally it is seen in the aorta This course of events is a little different from the course of events in non diabetic patients where it is usually said that the higher level arteries are the first involved Other pathologic features are usually the result of impaired blood supply, or ischemia These include atrophy and thinning of the skin, atrophy of the muscles with a replacement of fatty and fibrous tissue, loss of subcutaneous fat, replacement of fat by fibrous tissue, osteoporosis, and ischemic neuropathy The ischemic neuropathy is characterized by perineural fibrosis of nerve trunk and Wallerian degeneration of nerve fibers with demyelinization and occasional rupture of the axis cylinders Complete ischemia of tissue due to complete closure of arteries results in gangrene Such gangrene may follow slight trauma or slight infection in tissues already seriously ischemic

The physiologic disturbance in this condition is due to obstruction in the blood flow The ischemia will be proportionate to the extent of the occlusion and the size and number of branches which are shut off

In the diabetic, particularly the diabetic whose diabetes has begun early in life, there must be added important changes in the arterioles and capillaries In amputated legs of diabetic patients importance of the arteriolar hyalin change and arteriolar fibrosis is easily demonstrable Localized gangrene or severe limitation of the blood supply in one digit in the presence of good pulsation in the larger arteries is not rarely to be attributed in the main to arteriolar change rather than to the changes in the large vessels When this is present in such diabetic patients, one must also recognize the fact that arteriolar change is constantly a feature in the diabetic nephropathy and, therefore, this patient must be considered with due regard not only for

the condition of circulation in the lower extremities but also for his renal status and for the retinae

The symptoms in arteriosclerosis usually come on gradually as a result of a progressive limitation of blood supply due to obliteration of the arterial lumina, or suddenly as the result of arterial closure from thrombosis If the amount of the arterial tree occluded is small, symptoms may be slight or not at all However, progression in a series of events is more apt to be the case

Intermittent claudication is usually described as a cramp a pain, an ache or sense of fatigue in certain muscles, most commonly the calf muscles, developing after exercise The discomfort is quickly brought to an end by rest even if the patient does not sit down or lie down It occurs at some time in nearly all cases of arteriosclerosis obliterans, and in many patients it has been the earliest symptom Frequently it is unilateral, but may after months or years become bilateral In diabetic patients who come to the hospital with lesions of the feet it is uncommon for intermittent claudication to have been present for more than three years without some lesion of the foot developing Exceptions do occur and one can recall patients in whom there is a very definite history of intermittent claudication for five or more years without development of gangrene or other lesions traceable to this cause The claudication is most common in the calf, but also may be observed in the foot, thigh and lower part of the back The distance which the patient can walk will vary in different cases and will depend particularly upon the rate at which he walks The distance, in most patients is quite definite A patient may state that at an average pace he can only walk 100 feet before the pain develops If he walks very slowly and deliberately stops for a few seconds periodically, he may be able to walk for not only a good many blocks but sometimes a mile or more

Rest pain is the result of more severe interference with

blood supply and suggests an advanced type of the disease Commonly it is felt in the digits first but may occur in the foot or lower leg as well It is most common at night, interfering with sleep The patient often sits up in bed and rubs his foot for a considerable period of time Persistent pain after two or three weeks of complete rest is usually indicative of a very grave impairment of blood supply Pain of ischemic neuropathy extends over the major part of the leg and usually may be referred to the distribution of one or more trunks It may occur without ulceration or gangrene, it may be accompanied by numbness, deadness or coldness Even burning sensation may be complained of by the patient It is usually severe and difficult to relieve Paresthesias such as numbness, deadness, tingling or prickling, coldness or particularly burning are common Certain of these paresthesias occur frequently in diabetic patients even in early life without any evidence whatever of vascular disease Thus, the burning of the soles is a common symptom even in young diabetic patients who have no evidence whatever of vascular disease Complete anesthesia of the toes or feet, with or without muscular paralysis may occur after complete arterial occlusion

Muscular weakness, stiffness of the joints and sensitivity to cold are common complaints

Physical Findings

The physical findings of chief importance in the examination of diabetic patients are those of deficient blood supply The findings are, therefore, chiefly in the lower extremities Examination of the legs and feet of the diabetic patient should be carried out with the patient lying down and the leg bare from the hips to the toes Impairment of arterial pulsation found on careful and direct palpation is the most important physical finding in this condition as is also true of other occlusive arterial diseases Pulsations

should be sought and recorded first in the femorals, then in the popliteal, then in the posterior tibial and finally the dorsalis pedis arteries

Absence of pulsation in one or both femoral arteries is a serious indication of occlusion at that level or in the pelvic arteries or even in the lower aorta Examination at the knee should include a search for the external geniculate artery since pulsations palpable there usually indicate that the artery is forming an important pathway in the collateral circulation Popliteal pulsation may be felt for with the patient on his face and the legs extended Some physicians find it more easy to flex the knee and feel the pulsation with the knee flexed Absence of pulsation in one popliteal is an important finding, particularly if there are not pulsations felt below it and in the presence of symptoms of occlusion may indicate arteriography and consideration of surgical procedures, such as an arterial graft Pulsation in the dorsalis pedis artery is usually present under normal circumstances, but absence of palpable pulsation may not be a very significant finding since in a certain percentage, usually stated as 8, such pulsation is absent because of an anomaly of the arterial system Pulsation may also be felt in the anterior tibial, but absence of pulsation in the dorsalis pedis in a diabetic patient in the presence of symptoms is usually of significance It is certain that in diabetic patients, a considerable degree of atherosclerosis with even visible calcification by X ray, may occur without producing detectable impairment in arterial pulsations Such patients may not have intermittent claudication However, in some of those patients with good pulsations, the presence of claudication may be attributed to changes in the smaller arteriole

Color changes in the feet are of great importance One or both feet may be red, this change usually being most marked in the toes and less marked proximally Bluish areas or dusky areas over the foot may be present When recent occlusion has been present the foot may be pale and be

actually shrunken Color changes on change in posture are of great importance A foot which is abnormally pale on elevation and becomes red or cyanotic on dependency with delay in return of color usually indicates definite occlusive arterial disease If the time required for the filling of the superficial veins after dependency is prolonged beyond 15 seconds that also is usually indicative of vascular impairment If the feet are elevated for two minutes and the pallor does not give way to return of color within 15 seconds, that usually is a reliable sign of a moderate degree of arterial insufficiency Changes in temperature are usually demonstrable by a rough touch or by taking the temperature of the skin with a thermometer Trophic changes indicated by scarring and shrinkage of the digits, slow nail growth, failure to grow hair and pressure ulceration are serious indications of impaired blood supply Atrophy of muscles, skin and soft tissues are common findings When the legs are hung down oftentimes the atrophy of one leg as compared to the other is obvious Measurement will give definite quantitative data Induration of the muscles with weakness and loss of subcutaneous fat of the skin often go together

Osteoporosis in the infected limb, like atrophy, is an important sign

Edema of the foot and leg may occur, particularly when pain is severe, with or without ulcerative lesions Usually such patients have been sitting up at night in a chair because of pain or discomfort

Hyperesthesia and hyporeflexia may be noted in patients who have had recent arterial occlusion They also occur commonly in diabetic patients sometimes with slight or no degree of occlusive arterial disease

Infections of the Extremities

Infections of either the lower extremities or the hands of diabetic patients may result in the loss of a digit or

extremity despite good blood supply for several reasons In the first place, the organism recovered from the area of infection may prove to be highly virulent or resistant to antibiotics Secondly, the infection may overcome the patient's normal power of resistance because of the lack of control, emaciation, and the presence of ketosis of the diabetic himself Third, delay in treatment favors the development of extensive infection and, finally, some organisms not ordinarily pathogenic, appear to have pathogenic properties and the power of invasion in diabetic tissue The diagnosis of adequate blood supply rests upon the presence of good pulsations in the peripheral arteries secondly, excellent collateral circulation may be present in a foot even without palpable pulsations if the foot is normally warm well nourished and there is an absence of such symptoms as *intermittent claudication Gangrene may occur secondary* to infection and the local impairment of blood supply rather than primarily from occlusion of large arteries In this group of infections of the extremities, often a lack of normal sensation and sometimes actual anesthesia has led the patient to delay treatment Perhaps the most important single teaching which should be emphasized to diabetic patients is that a lack of pain when a toe or a hand is infected must not be interpreted as a favorable sign but rather as a warning that impairment of the sensation is due to serious nerve disorder

The treatment of infection involves first the diagnosis cultures to obtain the organism and to determine its sen*sitivity to specific antibiotics bed rest surgery* for the relief of pus or amputation of digits with osteomyelitis

Neuropathic Feet

In recent years the number of diabetic patients who present open lesions or recurrent ulcerations with reasonably good blood supply, but with evidences of the neuro

pathic background, have increased Thus, nearly one third of the patients seen at the Deaconess Hospital now show some type of neuropathy The outstanding features are the lack of sensation as determined by ordinary crude tests such as the testing with pinprick or perception of the difference between dull and sharp Measurements by the tuning fork will almost always show impaired sensation to vibration *Sometimes temperature sense is lost Anesthesia is sometimes* localized in certain areas and yet this is not easily referred to a single nerve pattern Sometimes anesthesia is so great that amputations of toes or even legs may be done without any anesthesia whatever Such feet are extremely vulnerable to pressure The wearing of new shoes may lead to blisters which will ulcerate, become infected and healing will take place only with rest in bed Lesions in such feet will usually heal with bed rest, but they tend to recur when the patient is on his feet or actively at work

Laboratory Studies

Roentgenograms

Examinations of the extremity by X ray in order to determine the presence of calcification in the arterial walls may have definite value in differentiating arteriosclerosis obliterans from other types of occlusive arterial disease, such as thrombo angiitis obliterans It should be noted first, however, that the presence of calcification alone is not proof of deficient blood supply *It is important to differentiate different* types of calcification seen in the vessels First, a rather finely divided calcification forming a thin line at the margins of the artery and usually seen in diabetics first low in the leg usually means calcification within the medial coat Although *this type of calcification is frequently seen* in the iliacs or femorals, it is commonly found as a first evidence of vascular change in young diabetics of many

years' standing who may show this lesion as early as the twenty fifth or thirtieth year It usually has no particular diagnostic value in indicating occlusive disease

When, in addition to much thicker deposits of calcium there are larger areas of calcium irregularly distributed even in the aorta, the arteries of lower extremity, and especially the lower leg, it usually indicates calcification in atheromas and may then be of some significance as an indication of an obliterating process Roentgenograms of the legs below the knee in diabetic patients frequently will show extensive areas of calcification, but even then usually this evidence is of less importance clinically than the clinical evidence of deficient blood supply obtained by direct examination of the extremity

Roentgenograms of the ankles and feet are essential as a means of recognizing presence or absence of bone atrophy, osteomyelitis or destruction of a joint, and especially in relation to the neurotrophic or pseudo Charcot joint

Blood Clinical Studies

Such analyses of blood and urine for sugar, CO_2 combining power, albumin, diacetic acid, acetone, non protein nitrogen will be needed in all diabetic patients as the clinical evidences of nephritis and acidosis indicate The relation of the volume of blood cells to plasma that is the hematocrit reading is often of real value particularly if there is any possibility of polycythemia being present

The determinations of the plasma lipid are often of value, particularly in diabetic patients who have been long under poor control They seldom aid in the diagnosis of the type of vascular disease, but may be of considerable importance as indicating the degree of disturbance in diabetic regulation and particularly the presence or absence of past ketosis

In our laboratory the upper values for normal in lipids per 100 cc of plasma are as follows cholesterol, 230 mg,

total phospholipids 270 mg , total of fatty acid, 400 mg , and total lipids 650 mg

In diabetics of long standing the electrocardiogram is done practically as a routine in patients who have occlusive vascular disease in the extremities Inasmuch as coronary arteriosclerosis is now the main cause of death in adult diabetics and is a most important single complication in diabetic surgery, electrocardiographic studies may be helpful in evaluating operative risk and particularly in influencing the judgment with regard to the type of therapeutic procedure and the likelihood of success Studies of skin temperatures may be helpful but their value has proven to be rather limited Similarly, the use of the oscillometer which has been recommended by some students as the best method for studying the degree of arterial pulsations, has in our experience had very limited value We first began to use the oscillometer 25 years ago and for a few years used it as an adjunct However as the years have passed it has proven to give very little information in addition to what may be obtained by careful palpation of the pulsations

Arteriography

These procedures may give valuable information as to the exact location of an occlusive arterial lesion If there is a localized occlusion and it can be demonstrated by X ray examination but below this localized occlusion reasonably good arterial supply is available to the foot, then surgical graft of an artery around the site of occlusion may prove to be of value At the Deaconess Hospital out of some fifty femoral arteriograms (1954), only a dozen actual surgical grafts have been carried out

Differential Diagnosis

The presence of occlusive arteriosclerosis obliterans may be established only by objective examination of the extremi

of both lower extremities is an outstanding finding Intermittent claudication may be unilateral or bilateral Pallor of the feet on elevation and other signs of ischemia are usually, although not always, found Occlusion of the anterior posterior tibial arteries is perhaps most frequent in diabetic patients 50 years and over In our dissection of amputated legs, practically always there has been found both atherosclerosis and medial arteriosclerosis in the tibial arteries It is true that when we compared the extent of the change in such diabetic legs as compared with non diabetic legs amputated for similar vascular disturbances, it appeared that the extent of the atheromatous change was much greater in the diabetic than in the non diabetic arteries

Acute occlusion of an artery results from sudden thrombosis in an atherosclerotic artery It may be the first clinical manifestation of disease, but in our diabetic patients it is a frequent occurrence in patients who have already had evidences of arteriosclerosis obliterans for many months

Prognosis For the diabetic patient who has developed arteriosclerosis obliterans with or without an open lesion the *outlook has become uncertain The condition,* although presenting symptoms in the extremities, is apt to be widespread, affecting particularly the coronary and cerebral circulation Hypertension is frequent and it increases the tendency to progression of the condition If diabetic retinitis is present, vision may be affected and the danger of a fall or fracture is increased as well as the likelihood of a renal lesion Sepsis is unusually frequent The many diabetic patients with this lesion are prematurely old and may have general debility, malnutrition and congestive heart failure Prognosis, therefore, on strictly medical ground is serious but may be vastly improved by good general care particularly in cooperation with the patient and his family Although diabetic patients with occlusive vascular disease have a shortened life expectancy, improvements have occurred in the last few years partly due to improved medical

care the new antibiotics and particularly the newer surgery

The results of surgery are vastly improved first with respect to conservation of the limb by more conservative procedures and second with respect to the prognosis Thus the use of sympathectomy selective treatment employment of toe amputations and trans metatarsal amputations in place of higher amputations have greatly reduced the frequency of amputations above the ankle The immediate results of amputations have improved to the point where 450 amputations for gangrene have a hospital mortality rate of only 5 per cent or less This mortality is almost inevitable on the basis of the coronary arteriosclerosis in such a group

Preventive Measures Against Ulceration Gangrene and Infection of Extremities

The importance of prophylactic measures for the prevention of lesions in diabetic feet is not sufficiently preached The careful examination of the feet at every visit of every diabetic patient past 40 years of age if carried out by the practitioner regularly would in itself emphasize what the patient will easily forget It is unfortunate that average diabetic patients are so often told that their diabetes is mild Actually it would be safer if the word "mild were never used in talking to the elderly diabetic because actually necrosis infection gangrene typically occur in the elderly patient with mild diabetes of long duration with inadequate diabetic treatment Earlier use of insulin and diet is the first step in prophylaxis

Trauma often slight is the precipitating cause of the majority of the ulcerative gangrenous lesions in diabetics with arteriosclerosis and ischemia in the feet The trauma may be mechanical chemical or thermal It may even be merely the pressure from an ill fitting shoe or prolonged use of a new and stiff shoe Usually it is minor The extremi

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Prognosis For the diabetic patient who has developed *arteriosclerosis obliterans with or without an open* lesion the outlook has become uncertain The condition, although presenting symptoms in the extremities, is apt to be widespread, affecting particularly the coronary and cerebral circulation Hypertension is frequent and it increases the tendency to progression of the condition *If diabetic retinitis* is present, vision may be affected and the danger of a fall or fracture is increased as well as the likelihood of a renal lesion Sepsis is unusually frequent The many diabetic patients with this lesion are prematurely old and may have general debility, malnutrition and congestive heart failure Prognosis, therefore, on strictly medical ground is serious *but may be vastly improved by good general care*, particularly in cooperation with the patient and his family Although diabetic patients with occlusive vascular disease have a shortened life expectancy, improvements have occurred in the last few years partly due to improved medical

care, the new antibiotics, and particularly the newer surgery

The results of surgery are vastly improved, first with respect to conservation of the limb by more conservative procedures and, second, with respect to the prognosis Thus the use of sympathectomy, selective treatment, em ployment of toe amputations and trans metatarsal amputa tions in place of higher amputations have greatly reduced the frequency of amputations above the ankle The im mediate results of amputations have improved to the point where 450 amputations for gangrene have a hospital mortality rate of only 5 per cent or less This mortality is almost inevitable on the basis of the coronary arterioscle rosis in such a group

Preventive Measures Against Ulceration, Gangrene and Infection of Extremities

The importance of prophylactic measures for the preven tion of lesions in diabetic feet is not sufficiently preached The careful examination of the feet at every visit of every diabetic patient past 40 years of age if carried out by the practitioner regularly, would in itself emphasize what the patient will easily forget It is unfortunate that average dia betic patients are so often told that their diabetes is mild Actually it would be safer if the word "mild" were never used in talking to the elderly diabetic because actually ne crosis infection gangrene typically occur in the elderly patient with mild diabetes of long duration with inadequate diabetic *treatment Earlier use of insulin and diet is the first* step in prophylaxis

Trauma often slight, is the precipitating cause of the majority of the ulcerative gangrenous lesions in diabetics with arteriosclerosis and ischemia in the feet The trauma may be mechanical, chemical or thermal It may even be merely the pressure from an ill fitting shoe or prolonged use of a new and stiff shoe Usually it is minor The extremi

of both lower extremities is an outstanding finding Intermittent claudication may be unilateral or bilateral Pallor of the feet on elevation and other signs of ischemia are usually, although not always, found Occlusion of the anterior posterior tibial arteries is perhaps most frequent in diabetic patients 50 years and over In our dissection of amputated legs, practically always there has been found both atherosclerosis and medial arteriosclerosis in the tibial arteries It is true that when we compared the extent of the change in such diabetic legs as compared with non-diabetic legs amputated for similar vascular disturbances, it appeared that the extent of the atheromatous change was much greater in the diabetic than in the non diabetic arteries

Acute occlusion of an artery results from sudden thrombosis in an atherosclerotic artery It may be the first clinical manifestation of disease but in our diabetic patients it is a frequent occurrence in patients who have already had evidences of arteriosclerosis obliterans for many months

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sequence of events, osteomyelitis following an infected corn is almost pathognomonic of diabetes The lesions result from excessive body weight, badly fitting shoes or a com bination of the two Calluses and corns should be relieved of pressure and especially be protected by shields which a competent chiropodist can provide Patients should be warned against cutting such lesions with any sharp instru ment unless they can use such an instrument as a surgeon does The soft corn seen between the toes is frequently an evidence of epidermophytosis The neurovascular corn con taining nerves and blood vessels is very painful The plantar wart, due probably to filterable virus is often infected and may prove a serious lesion Local astringents and particularly X ray treatment may be effective The danger of X ray burn must not be forgotten particularly if X ray treatment is used more than once

Epidermophytosis or fungus infection, often called ring worm or athlete s foot, is of greater importance in diabetes not because the infection itself is so serious but because it often represents a portal of entry for more virulent pyogenic organisms Injury of the lesion, pressure, and excessive per spiration invite trouble

Many diabetic patients should prepare for the night by taking exercises for five or ten minutes during the course of the evening These exercises may be carried out on a couch or a bed (Buerger vascular type)

Buergers Passive Exercises

Buerger, many years ago suggested certain passive exer cises were of value in producing hyperemia or rubor in the affected limb and therefore, therapeutically beneficial in increasing the blood supply If the method is carried out daily for a long period it is of real value in improving circulatory conditions In our experience at the Deaconess Hospital no one has felt that the Buerger exercises in and of themselves could produce a permanent anatomic change

2 Avoid strong irritating antiseptics such as sulpho naphthol and iodine
3 At once after injury some surgeons recommend applications of sterile gauze saturated with medicated alcohol or hexylresorcinol (S T 37) *Keep wet for not more than thirty minutes by* adding more of the antiseptic solution Sterile gauze in sealed packets may be purchased at drug stores
4 Elevate, and as much as possible until recovery, avoid using the foot
5 Consult your doctor for pain, redness swelling or any inflammation

Epidermophytosis

Special Directions Regarding Care of the Feet

Many people are affected with itching, scaling cracking or blisters on the feet especially between the toes This condition is often a ringworm infection or epidermophytosis It is a common infection and at least 60 per cent of all persons have it at some time It is particularly objectionable in diabetics, because it itches and scratching may give opportunity for other more dangerous infections to gain entrance The disease is usually picked up by walking barefoot on the floors of common shower baths, dressing and locker rooms, infected bath mats or any floor or floor covering where others have walked in their bare feet

The disease most commonly shows itself as a slight cracking or scaling giving the appearance of dead, white skin between the fourth and fifth toes The so called soft corn is one form of this infection In more severe cases groups of small deep blisters come on the soles of the feet and the palms of the hands This form usually itches intensely Most cases are worse during hot weather or when wearing shoes and stockings which heat the feet

Calluses, Warts, Corns and Fungus Infection

Calluses and corns are common lesions and frequently the site of infection leading to osteomyelitis Indeed, this

45 degrees or 60 degrees as desired Patients may spend from three to six hours daily in doing these exercises

All vaso-constricting influences should be avoided The use of tobacco is contra indicated in diabetic patients with occlusive vascular disease as well as for the danger to the eyes Although tobacco may not be so serious in its implica tions as in cases of thromboangitis obliterans nicotine is a vaso constrictor which should be completely and perma nently omitted Exposure to cold should be avoided

Treatment

The Attitude of the Physician toward the Problem Pre sented by the Elderly Diabetic with Arteriosclerosis Ob literans Will Be Affected by Several General Considerations

1 The impairment of blood supply is due to organic arterial obstruction and to reduction of the lumina of many arteries At present only direct arterial surgery applicable to only a few people actually removes such organic obstruc tion

2 Although with careful management there may be no progression in some patients for many years actually usu ally the arterial disease progresses steadily or irregularly once it has been clinically evidenced In favorable cases and particularly among diabetic patients there is seen with some frequency striking improvement in the collateral cir culation If such patients can by good care avoid infection or trauma to the feet and avoid ischemia from postural or local causes improvement in the peripheral circulation may take place over a period of months or years which wi result in the disappearance of intermittent claudica improved ability to walk and indeed improved abi heal minor or superficial lesions

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in the blood vessel or could relieve the progression of the sclerotic process Therefore it may fairly be said that the Buerger exercises are not curative On the other hand, over the years, we are convinced that the patients who have occlusive vascular disease with ischemia are helped by carrying out these exercises, first, because they provide a period of rest when the patient is off his feet at least three or four times a day Secondly, periods of hyperemia are beneficial Third, patients who are recovering from a thrombosis seem to develop a re-establishment of collateral blood supply a little more satisfactorily while they are carrying out Buerger exercises over a period of some weeks

"The affected limb is elevated with the patient lying in bed, to from 60 to 90 degrees above the horizontal, being allowed to rest upon a support for thirty seconds to three minutes, the period of time being the minimum amount necessary to produce blanching or ischemia As soon as blanching is established, the patient allows the foot to hang down over the edge of the bed for from two to five minutes, until reactionary hyperemia or rubor sets in, the total period of time being about one minute longer than that necessary to establish a good red color The limb is then placed in the horizontal position for about two to five minutes, during which time an electric heating pad or hot water bag is applied, care being taken to prevent the occurrence of a burn The placing of the limb in these three successive positions constitutes a cycle, the duration of which is usually from six to ten minutes These cycles are repeated over a period of about one hour, some six to seven cycles constituting a seance"

The Buerger boards used at the Deaconess Hospital consist of two boards, each ¾ inch thick, 30 inches long, and 11 inches wide, hinged at one end In the middle of one board is a hinged tongue with a cleat on the other board so that the boards can be opened at an angle of 30 degrees,

fat sometimes may be used in patients with severe hypertension In patients at the Deaconess Hospital measurements of the lipoproteins by the technique of Gofman and associates has indicated that values were highest in patients whose diabetes was least well controlled and that these values could be reduced rapidly over a period of weeks with the adequate use of insulin and a diet restricted in lipids

Drug therapy in the past has included thyroid extract and estrogens Thyroid extracts seem to have some influence upon hypercholesteremia Phytosterol has been used to reduce high concentration of cholesterol in both humans and animals This is a sterol obtained from soy beans Its use on our diabetic patients has been limited to such a small number that conclusions are not yet possible Other agents with lipotrophic effects include choline and inositol but as yet significant clinical effects are not clearly demonstrated Heparin has been used experimentally because of its well known power to reduce the number and concentrations of large lipoprotein molecules in the blood In a series of patients with intermittent claudication studied for a period of some months at the Deaconess Hospital the effect of heparin upon the lipoproteins and more significantly upon the claudication was too variable to permit a very definite conclusion at this time

Vasodilators

In patients with evidence of vasospasm indicated by moisture in contrast to dry skin typical of the diabetic patient with arteriosclerosis procedures aimed at vasodilatation may be considered Thus regional sympathetic ganglionectomy is the most effective method of producing persistent vasodilatation The operative mortality has been greatly reduced It does not cure the disease but merely makes possible the release of the sympathetic tone and permits vasodilatation particularly of the small vessels chiefly near the surface

of the common evidences of senility, it is apt to be accompanied by much more extensive and widespread arteriolarsclerosis and therefore may be complicated by the diabetic nephropathy or diabetic retinitis

4 Finally, today the most regrettable disasters are those in which major surgery with the loss of the leg has become necessary because of the failure to recognize serious occlusive vascular disease as the underlying factor in ulcerated lesions of the toes Therefore, needed hospital observation and study was not provided at the time when amputation of toes or through the transmetatarsal area under appropriate conditions would have saved a walking foot

Medical Measures

Diabetic diet together with insulin is basic, first, for controlling the diabetes and, second, for controlling the abnormal lipoid metabolism which may itself be directly involved in the progression of the atherosclerosis The importance, therefore, of the lipoid content of the diet is today being restated It has been a subject of considerable study and there is still much lack of agreement among investigators Although it appears that limitation of the dietary cholesterol alone may not be sufficient to influence the level of cholesterol in the blood, there is increasing evidence indicating that in many individuals a reduction in the total amount of fat consumed per day will reduce the level of plasma cholesterol and, indeed, the level of blood lipid It should be stressed, however, that in diabetic patients who show under many circumstances high levels for lipids especially during ketosis, it is the use of insulin itself which will produce, as diabetes is controlled, a much more rapid decline in hyperlipemia than any other single agent It is the combination, therefore, of a diet plan for restriction of lipids together with the use of insulin, which in the diabetic patient is most apt to have a favorable effect upon the lipid metabolism The rice fruit diet which contains almost no

week for the next four weeks Our experience at the Deaconess Hospital, however, has led us to give up such injections In obese patients reduction in weight is important. Patients should be advised to walk slowly and to stop soon or preferably just before claudication occurs Some muscular activity is advisable, but certainly patients should be urged not to force themselves to walk after pain has developed The pain and discomfort of ischemic neuropathy are difficult to control If complete rest in bed for two or three weeks does not give control, if surgical lesion is present, it implies more serious limitation in blood supply large doses of vitamins including thiamine, vitamin B-12 and liver extract have been tried but with doubtful effects For rest pain, particularly during the healing of the sluggish ulceration, the position of the patient in bed is of extreme importance Thus, all such patients should lie in bed with the chest and head raised at such an angle that the heart is definitely above the level of the leg Often it will be found that the head of the bed should be raised on blocks and the foot involved may need to be dropped a little lower than the other foot in order to find that angle at which circulatory efficiency is greater Without definite measurement of the time necessary to secure the best color of the affected foot, it is possible for a patient lying flat in bed or with the head only slightly raised to have the toes or, indeed, a large part of the foot really ischemic during a greater part of the 24 hours Certainly prolonged sitting by the patient with the feet hanging down is bad, first, because it results in stasis and, secondly, because it favors othostatic edema and further impairment in circulation Drugs such as barbiturates may be helpful for sleep but often have to be reinforced with salicylates, opium or demerol

The use of such drugs as hexamethonium bromide to improve the peripheral circulation by partial blocking of the sympathetic nervous system has been given extensive trial

Nerve blocking by injection of alcohol is useful as a diag nostic measure only In patients who have occlusive vascu lar disease, the use of drugs such as alcohol or priscoline is not indicated Studies of skin temperature and other studies indicate that priscoline may be useful in persons with normal extremities, but that it has no benefit in patients who really are suffering from occlusive vascular disease

Mechanical Measures

The Sanders Oscillating Bed The use of this bed is in tended to produce an improvement in blood flow by alter nately raising and lowering the lower extremities above and below the level of the heart without any effort on the part of the patient It has advantages, therefore, in patients whose general physical state prevents them from giving as much cooperation as is desirable For some patients who have serious impaired circulation, particularly with severe rest pain the use of the bed seemed to bring relief of pain and at least temporary improvement in circulation Trials with this bed resulted in our giving it up since we found so few patients in whom it gave any better result than the use of the postural exercises It certainly should not be used in patients where there is real gangrene and also where there is very much local or extending infection

Postural exercises of the Buerger type have already been described

Intermittent pressure and suction and intermittent venous occlusion are two methods which were given thorough trial for a number of years but have been pretty generally abandoned

Treatment of Pain

For intermittent claudication injections of tissue extract, particularly pancreatic tissue extracts given intramuscularly have seemed to be of some value Such injections have been given, one injection a day for a week, and two injections a

used as a solution or as an ointment (chloresium ointment). No very striking benefit has been observed in our patients

Anticoagulants

The use of anticoagulants need not be reviewed here since an extensive literature on their use is available Our experience is confined largely to heparin and dicumarol We have used it in patients with coronary occlusion, acute venous thrombosis, pulmonary embolism and sudden arterial occlusion Heparin has been given intravenously in injections of 50-75 mg every 4 6 hours or subcutaneously during the night Heparin has been used until its anticoagulant effects were replaced by the effect of dicumarol

Heparin was discovered in 1916 It is a mucopolysaccharide of high molecular weight It acts on thrombin, prothrombin, thrombokinase and other substances The method of continuous intravenous infusion was tested by Murray and Best They use a physiologic solution of sodium chloride containing 10 mg of heparin in each 100 cc diluted They permitted the solution to flow into a vein by the gravity method of flow It was desired to prolong the coagulation time between two and three times the normal Intermittent intravenous injection has been employed at various times The intramuscular and subcutaneous routes have also been employed Heparin has been used in a menstruum on many occasions The usual experience is that wide fluctuations and difficulty in control can be avoided by the intermittent method

Dicumarol (4 hydroxycoumarin)

The indications and contraindications for the use of dicumarol are varied Among diabetic patients a certain group seem to be extremely sensitive to dicumarol Severe hemorrhage has followed its use in comparatively small doses in several instances We, therefore, usually begin the

There are hazards in its use Intra-arterial injections and histamine have not been used sufficiently to justify their use Previous reports that histidine, vitamin C and ether are of value have not been confirmed Peritrate is stated to improve intermittent claudication, but our experience has not left us with much enthusiasm

The Application of Local Agents

Any preparation used locally in diabetic patients for ulcerations or infections resulting from either arterial or venous insufficiency must be non irritating and non cytotoxic One of the great difficulties is that as each of the new agents are brought forth, and this is notably true of the sulfa drugs, the delicate diabetic skin proves to be so sensitive that the most irritating results are seen Basically, in the diabetic patient except for purposes of cleanliness and protection, it may be said that the influence of any external application is extremely limited The local application of antibiotics which are specific for the organism found by culture may at times be advisable Ointments containing local anesthetic, although they may give comfort, are often dangerous since they are frequently cytotoxic Preparations containing phenol or cresol, even in small percentages, should never be used because of their extremely cytotoxic properties and the danger of inducing gangrene

On the other hand, boric acid solution is not cytotoxic and it is, therefore, relatively safe Although boric acid solution is only weakly bacteriostatic, it can be used as a warm application for short periods, 1 5 times a day, with benefit for superficial infections or gangrenous lesions A solution of penicillin may be applied in a continuous wet dressing in cases with superficial infections or for organisms sensitive to penicillin The use of varidase among the diabetic patients is still under study Chlorophyll has been reported useful in the treatment of chronic ulcers of the leg when

extremities has been observed in our cases with such drugs as Priscoline, Etamon, etc.

e Diathermy and ultraviolet ray treatment were once employed for local effect but in the diabetic of long duration danger of burns is genuine

3 Procedures in the Presence of Ulcers or Superficial Gangrene

a Hospitalization and bed rest The benefits of complete rest are almost never realizable under conditions of home treatment

b The use of penicillin, sulfonamides or other antibiotics

c Local application such as sulfathiazole ointment, solutions of tyrothricin streptokinase-dornase may be selected for individual cases

4 Procedures in Gangrene of Toes, Osteomyelitis or Infection Involving Joints

a Same plan of treatment as in 3 Closest cooperation between physician and an experienced surgeon Emphasis upon early diagnosis and surgical decision Procrastination in the diabetic in the presence of arteriosclerosis obliterans and severe infection will result in costly delay

b Conservative surgery such as the transmetatarsal amputation in an early stage may preserve walking when an amputation of a single toe would otherwise be followed within 12 to 24 months by a lesion on other toes and subsequently thigh amputation

5 Methods in Cases with Gangrene Extending Into the Foot or Leg

a Amputation of the leg.

6 Procedures in Cases of Acute Arterial Occlusion

a. Immediate consultation in a hospital within the shortest possible time for decision as to whether embolism is present. The surgical removal of an embolus in the large artery of the leg has the best chance of success the more quickly the operation is carried out

b Bed rest with the head of the bed slightly elevated is desirable in all cases with deficient blood supply in the leg

c. Loose wrapping of the foot and leg in sheet wadding Use no local heat Actual cooling of the leg with a fan may be employed

d Dicoumarin

e Intravenous injection of papaverine

f Heparin by vein may be continued until the effect of Dicoumarin is obtained.

use of anticoagulants with moderate doses of heparin at the same time we start with 50-100 mg of dicumarol We avoid the use of dicumarol after recent operations, not only in the brain and spinal cord, but in patients where there is any suspicion of any impaired liver function or in patients who have been recently actually bleeding As an antidote for dicumarol, therapeutic doses of synthetic vitamin K_1 and K_1 oxide have been used When 0 5 gm of K_1 oxide is injected intravenously, at about 4 hours marked hypoprothrombinemia changed to moderate hypoprothrombinemia An average of 13 hours may elapse after injections of 4 prothrombin times are consistent with intravascular clotting

Outline of Treatment

The following outline summarizes methods of treatment commonly employed

1 The General Procedures Applicable to all Diabetics with arterio sclerosis obliterans
   a Detailed instruction of the patient as to the nature of the two diseases and the protection of his feet from specified types of injury, such as burns from thermal or chemical sources and other traumata
   b Dietetic treatment with low fat and low cholesterol diets
   c Control of diabetes by proper diet and adequate use of insulin
   d Reduction of weight by a diet planned to avoid too rigid curtailment of carbohydrate
   e For intermittent claudication sympathectomy in selected cases, (a) when evidence of overactive sympathectic inner vation is present, (b) when general condition permits
   f Buerger exercises two or three times a day
   g Tobacco should not be used

2 Treatment in Cases with Rest, Pain or Ischemic Neuritis without Gangrene
   a Hospitalization with bed rest in a warm room
   b Mechanical treatment with intermittent venous compression
   c Sedation for relief of pain Vitamin B_{12} as trial
   d Vasodilators and tissue extracts may be tried but in cases with true occlusive vascular disease no lasting benefit or evidence of persisting vasodilation and increased blood supply to the

Case I (38093) A 23 year-old lady in the 32nd week of her second pregnancy was admitted because of abdominal pain, nausea and vomiting The evening before admission she had her usual supper, felt nauseated and had three attacks of diarrhea during the evening The next morning she felt weak and because of this she did not take her insulin Nausea persisted and on the morning of admission she induced vomiting Following this she vomited small amounts of bile stained material three or four times Upon admission the blood pressure was systolic 105, diastolic 85 and the pulse 100 The abdomen was distended with an enlarged uterus compatible with a 32 week pregnancy The fetal heart was not heard but later it was heard and the patient felt reasonable fetal activity The white count was 17,900 *with 93 per cent polymorphonuclear The CO_2 of the plasma* was 22 mEq and the blood sugar was 66 mg per cent. Mild ketonemia was present She now had pain low in the right flank The obstetrician felt that acute hydramnios existed The surgical consultant doubted the existence of appendicitis The lower abdomen was tender all over The third day she had amniotomy with the release of only 150 cc of amniotic fluid The temperature up until this time had varied between 98 99 degrees The third day the temperature rose to 102 4 degrees A laparotomy disclosed an acute, gangrenous appendicitis The appendix was long retrocecal, lying along the course of the right ureter Almost complete rupture of the uterus was also present through the previous Caesarean section scar Appendectomy was performed followed by a Caesarean section which released an almost dead baby who lived only four hours Hysterectomy was performed Her postoperative course was stormy, but she made a complete recovery and was discharged on the fourteenth day

Case II A male, age 68, with diabetes of 14 years' duration was admitted for treatment of gangrene of the right

g If gangrene develops as is true in the majority of older diabetic patients, amputation at a level to be decided after the effect of Dicoumarin has worn off

OTHER CONDITIONS SURGICALLY TREATED

Appendicitis

The difficulties presented in attempting to distinguish between abdominal pain due to diabetic acidosis or diabetic coma, from pain due to a surgical lesion within the abdomen and impending acidosis or coma, require a careful analysis of various facts in the history, physical examination and laboratory findings in each case Not many cases have been reported in detail and very little discussion of the diagnostic difficulties has been presented The number of cases reported where actual operation was done and no demonstrable pathology found is small, and the number undoubtedly does not represent the number of such operations Also, it is undoubtedly true that many patients with acute appendicitis or other emergency surgical lesions of the abdomen have been refused operation or have had operation postponed because of the confusing presence of diabetic acidosis Among 60 cases with diabetes and operation for acute appendicitis at the New England Deaconess Hospital, certain features of the problem have presented themselves very clearly Thus, among diabetic patients with or without the presence of diabetic acidosis or impending coma, the number of patients who prove to have atypical *acute appendicitis is strikingly large* Thus, the onset of acute appendicitis with diarrhea or with nausea without pain or the absence of leukocytosis and the absence of fever have been frequent Case #5732 entered the hospital in diabetic coma with no history of pain, recovered from coma only to die 21 days later Autopsy showed an unsuspected appendix abscess as the cause of death The following three cases are illustrative

History and Physical Findings in Diabetic Acidosis and Coma

Study of the records of patients with acidosis with associated abdominal pain emphasizes certain facts of great importance in attempting a differential diagnosis When an accurate history is available, usually patients who are in diabetic acidosis have had nausea and vomiting as early symptoms Later drowsiness or dyspnea and air hunger indicate acidosis which has reached a rather severe degree Usually, it is true that in diabetic acidosis and coma nausea and vomiting precede the pain The pain may, however, in some cases be first The pain of diabetic acidosis usually in the upper abdomen but sometimes mid abdominal and even occasionally in the lower abdomen may be intermittent or steady, and occasionally may be so severe as to cause the patient actually to writhe in agony It may be accompanied by widespread muscle spasm and tenderness A board like abdomen may be seen even in children Usually, however, it is one of the first symptoms to disappear under adequate insulin treatment and usually marked improvement can be brought about in the muscle spasm and pain within 3-6 hours A dilated stomach is common in diabetic coma and may reach enormous proportions It may give rise to upper abdominal symptoms Visible peristaltic waves may be noted Hemorrhage, which is common in such a dilated stomach, will give rise sometimes to bloody vomitus, but more commonly to the dark brown gastric content commonly removed by gastric aspiration The leukocyte count in diabetic coma is usually elevated Levels of 25,000 to 40 000 per cubic millimeter are common Case 8741 entered the hospital with a white blood count of 97,750 but this dropped within 24 hours to 20,000 This leukocytosis has not been satisfactorily explained although it has been attributed to the distention of the liver capsule or to obstipation How-

foot Seven years previously he had had a left supracondylar amputation for gangrene of the left foot For six weeks he had had an ulcer on the right great toe which had increased in size and had become gangrenous Amputation of the leg below the knee was carried out on the fourth day. Diabetic control was no problem as he required only a small dose of 18 units of insulin On the sixth hospital day his temperature, which had been normal the previous five days, reached a level of 100 degrees at 8 P M On the seventh day the temperature reached 100 8 degrees Examination at that time disclosed no abnormality The next morning the white count was 24,900 At 6 A M on the eighth postoperative day he was seized with severe abdominal pain and was found to have an acute surgical abdomen with board-like rigidity suggesting a ruptured viscus Operation was immediately performed by Dr Clifford Franseen who found a generalized peritonitis from a ruptured appendix In spite of drainage and the use of antibiotics, he remained in shock and died in 36 hours

Case III A female, age 26 years with diabetes of 12 years' duration, developed nausea and vomiting without abdominal pain During the next few days nausea was intermittent and she began to have some vague abdominal pain which did not seem sufficient to secure the services of a physician However, on the seventh day pain, nausea and vomiting were more severe and she was sent to the hospital with a question of diabetic acidosis On admission she had no diabetic acidosis but the abdomen was tender to palpation, there was generalized muscle spasm and rigidity At operation she was found to have a perforated appendix with generalized peritonitis Her condition was grave during the next three weeks She received intensive treatment with antibiotics, was fed continuously by vein A large collection of pus under the diaphragm was evacuated on one occasion She was discharged with recovery after a four months' stay.

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foot Seven years previously he had had a left supracondylar amputation for gangrene of the left foot For six weeks he had had an ulcer on the right great toe which had increased in size and had become gangrenous Amputation of the leg below the knee was carried out on the fourth day Diabetic control was no problem as he required only a small dose of 18 units of insulin On the sixth hospital day his temperature, which had been normal the previous five days, reached a level of 100 degrees at 8 P M On the seventh day the temperature reached 100 8 degrees Examination at that time disclosed no abnormality The next morning the white count was 24,900 At 6 A M on the eighth postoperative day he was seized with severe abdominal pain and was found to have an acute surgical abdomen with board like rigidity suggesting a ruptured viscus Operation was immediately performed by Dr Clifford Franseen who found a generalized peritonitis from a ruptured appendix In spite of drainage and the use of antibiotics, he remained in shock and died in 36 hours

Case III A female, age 26 years with diabetes of 12 years' duration, developed nausea and vomiting without abdominal pain During the next few days nausea was intermittent and she began to have some vague abdominal pain which did not seem sufficient to secure the services of a physician However, on the seventh day pain, nausea and vomiting were more severe and she was sent to the hospital with a question of diabetic acidosis On admission she had no diabetic acidosis but the abdomen was tender to palpation, there was generalized muscle spasm and rigidity At operation she was found to have a perforated appendix with generalized peritonitis Her condition was grave during the next three weeks She received intensive treatment with antibiotics, was fed continuously by vein A large collection of pus under the diaphragm was evacuated on one occasion She was discharged with recovery after a four months' stay

history of abdominal pain which is the cause of the acidosis and coma Finally, in diabetic patients the onset of acute appendicitis is often atypical Unfortunately, it is the patients with an atypical onset in whom delay in carrying out proper surgical procedures occurs which result in the present death rate Whenever a diabetic patient vomits or is nauseated, although one must first think of diabetic acidosis, appendicitis or some acute surgical abdominal lesion must be considered and ruled out. The patient should be admitted to a hospital for observation and the necessary laboratory studies for the determination of the presence or absence of diabetic acidosis, leukocytosis and other necessary steps In rare cases where definite differentiation is impossible and yet necessary, it may be safer to open the abdomen under local anesthesia than to permit further delay

ever, experimentally, it is possible to produce such leukocytosis by severe dehydration in animals

When acute pancreatitis is present, diabetic coma often follows Occasionally, in such patients sweating due to the shock of the acute pancreatitis has been present when usually in true diabetic coma the skin of the axillae, the tongue and the body generally are extremely dry Pancreatitis, however, is a rare complication

Cases with diabetic acidosis and negative findings at operation have been reported Usually the pre operative diagnosis, because of the severity of the abdominal symptoms, has been acute pancreatitis, perforated peptic ulcer or perforated appendicitis

Abdominal Emergency Operations

In the cases studied at the Deaconess Hospital, the preoperative diagnosis has been acute appendicitis with the exception of two cases with perforated duodenal ulcer, one case of acute salpingitis, one case of acute regional ileitis and three cases of acutely inflamed glands in the mesentery of the terminal iliac The signs and symptoms may be masked by the diabetes and acidosis rather than exaggerated and the diagnosis is often made not because of the widespread signs and symptoms, but rather on the less than usual local tenderness In a summary by Dr L S McKittrick certain important conclusions were made 1 Cases operated upon with negative findings had usually had a preoperative diagnosis of extensive surgical lesions such as acute pancreatitis, general peritonitis or perforated ulcer 2 In all cases where the diagnosis of acute appendicitis was made, whether acidosis was present or not, the history of pain associated with localized tenderness and spasm was found 3 The history from his family when it was not possible from the patient, often suggests that in the patient without demonstrable lesions, the early symptoms are really those of coma which precede the onset of pain rather than a

damage has been demonstrable Although this accident can occur any time during pregnancy, it tends to peak in the 36th week Intrapartum deaths have occurred when the obese, edematous infant has been extracted with difficulty through the edematous pelvis Often the head is extracted without difficulty but the shoulders have jammed making extractions difficult or even impossible Neonatal deaths appear to be largely respiratory in nature

With this background, we have established four goals in our management These are obvious ones The first goal is maternal survival Our problem is concerned not only with a period of pregnancy but with the next 20 consecutive years It is a social tragedy to permit these young diabetic women to complete pregnancies with live born infants, but survive the pregnancy for not more than a five year period A prognosis for long life cannot be assured at present in these patients for, with all our experience, we have only 85 former juveniles who have survived 35 years of their diabetes Many of our young diabetics have had the disease for 20 25 years at the time of the first pregnancy Therefore, the second objective has been to prevent the precipitation or acceleration of vascular damage Abnormal pregnancy, especially toxemia, as well as diabetes, makes this woman susceptible to vascular disorders of the retina and of the kidney The third objective is again the obvious one —the increase of fetal salvage and the fourth has been a program for the prevention of diabetes in the offspring of the diabetic parent

The methods which we have found helpful in obtaining these objectives number seven as follows First, a classification of patients for fetal hazards Second, the very best possible chemical control of diabetes Third, the controversial part of the problem, the use of female sex hormones Fourth, measures used to prevent edema and hydramnios Fifth, early and accurate timing of the delivery Sixth, special care of the infant in the neonatal period, and seventh,

CHAPTER XVII

DIABETES AND PREGNANCY

Today two schools of thought exist for the management of the obstetrical diabetic patient The first school stresses chemical control of diabetes, and states that fetal survival is assured by good treatment of this disease The second school of thought, although favoring chemical control of diabetes, argues that this is no guarantee for fetal salvage and that additional forms of therapy must be given We belong to this latter school of thought and believe that poor chemical control of diabetes, hormonal imbalance and vascular lesions affect the course and outcome unfavorably

The potentially malignant nature of the combination of pregnancy and diabetes was shown decisively in the pre-insulin era when few diabetic women conceived and the few who conceived rarely survived pregnancy The harmful effect of diabetes upon fetal salvage was shown just as decisively in the insulin era for most reports indicate that spontaneous abortion, intrauterine, intrapartum, and neonatal deaths occur in more than half of diabetic pregnancies The characteristics in course and outcome are well established Thus, the spontaneous abortion rate has been some twice that of the general population Premature deliveries have occurred most commonly in those patients where the degree of hydramnios has been excessive and where apparently for mechanical reasons the membranes have ruptured prematurely The mature appearing but immature infant has not been able to survive its prematurity Intrauterine deaths have occurred most commonly as a complication of toxemia of pregnancy or where chronic vascular

tion Vascular damage is not demonstrated but may exist in a latent state Class D includes those patients whose diabetes is of more than 20 years' duration after which time the absence of vascular damage is unlikely, or those whose onset occurred under the age of 10 or patients regardless of age at onset or duration who have developed vascular lesions of the earliest clinical varieties, namely the retinopathies or calcifications of the vessels of the legs Probably under the same heading should be our Class E, which has been separated because it was the first to attract our attention to the importance of vascular damage in pregnancy, namely, those patients where the vascular damage has progressed so far that the vessels of the pelvis can be demonstrated to contain calcium by X ray Although this suggests medial sclerosis, the characteristic of diabetes is intimal sclerosis in vessels ordinarily involved with the medial type of lesions Although the iliacs are the vessels usually shown, we believe that the ovarian and uterine arteries are similarly involved and in the autopsied cases this concept has been confirmed Class F, a dreaded group by any standard, includes those patients with albuminuria not accounted for by pyelitis or acute nephritis This is a group of young diabetics whom we are sure have intercapillary glomerulosclerosis or the Kimmelstiel Wilson syndrome

The validity of this classification depends upon the relative fetal survival rates If we study the entire period of pregnancy where one expects a fetal salvage of some 87 per cent, we have found the following in Class A, 100 per cent, Class B, 67 per cent, Class C, 48 per cent, Class D, 32 per cent, Class E 13 per cent and Class F, 3 per cent These results were found in a group of 278 cases where the management consisted of good chemical control of diabetes and the best available obstetrical management but no female sex hormones Much of the controversy in the obstetrical diabetic literature today concerns differences in types of patients treated and reported Thus, today our most common

yearly followup of these children for a disturbance of carbo hydrate metabolism forever after

The classification which we have found helpful is based upon the age at onset, the duration of diabetes and the presence or absence of vascular lesions It presupposes that diabetes with onset in childhood is of a more malignant nature than that which occurs in adult life Measured in insulin production, this group of patients represents total or *near total diabetes With their complete dependence upon* exogenous insulin, chemical control of the disorder is more difficult Exogenous insulin cannot regulate itself according to tissue sugar level The second basis for classification is that vascular damage is unlikely under 10 years of duration of diabetes but that after 20 years only one young patient in 10 and after 25 years only one in 50 can be found completely free from at least minimal evidence of vascular damage, and, finally, that vascular damage in the diabetic carries with it the same hazards as vascular damage in the pregnancies of women in the general population The designation of the classification we employ is alphabetical, Classes A through F Class A consists of subclinical diabetics, those patients in whom the diagnosis of diabetes is made upon the basis of a glucose tolerance test which differs but little from *normal It is not the practice of diabetic clinics to* administer a glucose tolerance test if the diagnosis can be established on random blood sugars so these patients have minimal disturbance In the majority of our patients the glucose tolerance test has actually been done in the non pregnant state These patients under ordinary circumstances do not require insulin and need very little dietary regulation Class B includes patients whose onset of diabetes has occurred in adult life but where the duration is so short, under 10 years, that vascular damage is unlikely and is not demonstrable Class C includes the patients the onset of whose diabetes occurred in adolescence at 10 19 years of age or where the duration of diabetes is between 10 19 years' dura-

renal threshold for glucose is low and the excretion of sugar is disproportionately high It is, therefore, often difficult to prevent patients from developing either ketoacidosis or severe insulin hypoglycemia We have favored the use of one of the intermediate acting insulins, Lente or NPH or Globin insulin mixed with regular insulin In the third trimester we often supplement with regular insulin before lunch before supper and even at bedtime The caloric prescription obviously must be adequate We plan 30 calories per kilogram of increasing body weight, but at the same time try to maintain the weight gain to below 15 pounds so that in the third trimester the patient may receive a caloric prescription below that of the first trimester The carbohydrate should be fairly liberal, 180 250 grams (it has been estimated that the fetus metabolizes 50 grams of glucose in the third trimester) the protein high, up to 2 grams per kilogram, and the fat merely to complete the caloric prescription

SPECIAL INSTRUCTIONS GIVEN TO THE PREGNANT DIABETIC

Acute Illness

Every two hours for 7 feedings take any of the following in 6 ounce portions Milk fruit juice eggnog ginger ale or Coca Cola

Continue usual insulin and also test at 11 30 a m 4 30 p m 10 00 p m and according to test take immediately of crystalline insulin 12 units if the test is red brown or orange (2% on clinitest) or 8 units if yellow (1% on clinitest)

Diarrhea

Replace each portion of fruit with one glass of boiled milk (to be taken with teaspoon), each portion of 3% or 6% vegetables with one Uneeda or similar biscuit, and replace one portion of meat with an egg or cottage cheese or if severe, 2½ quarts of boiled milk and nothing else

Tests

Acetone Use tablet or powder

Quantitative Sugar Collect 24 hour sample Multiply per cent sugar obtained by clinitest by volume of urine in cc—this equals grams of sugar lost.

Example 2000 cc x 0 5% equals 10 grams

class is D and 70 per cent of our patients are in classes C through F

A few general statements may be made about these classes Class A can usually be handled as women without diabetes, although we consider Class B a mild group, it has proved a plaguing one for the obstetricians These patients have many insulin producing cells and suffer much more from the diabetogenic action of pregnancy than do women whose diabetes is actually more severe at the start of pregnancy During pregnancy these milder diabetic patients develop severe types of diabetes with which they are unfamiliar, and unless they receive constant medical attention *they develop ketoacidosis or severe hypoglycemia* Ketoacidosis, in the second trimester particularly, carries with it a very high fetal mortality rate It is this group of patients, where the duration of diabetes is short and where presumably those factors operative in the production of diabetes are still active, who tend to produce the largest infants Again they plague the obstetrician when pelvic delivery is attempted, for the head is extracted without difficulty but the short neck and the wide shoulders frequently cause obstetrical difficulties Classes D, E and F prove to be treacherous from the point of view of intrauterine deaths in week 36 These women tend to produce small infants, and in spite of the duration of diabetes they are more favorable candidates *for pelvic delivery than are those of short* duration Because these patients have had experience in the management of the most malignant type of diabetes, they know how to manage the severe problems and the difficult problems which arise in pregnancy better than those women who under ordinary circumstances have a milder form of the disorder This classification has, therefore, helped us in individualizing both medical and obstetrical management

Chemical control of diabetes is most certainly an objective in the management of these patients It is often difficult because the placental hormones, ACTH, *cortisone and* growth hormone are expected to intensify diabetes In addition, the

renal threshold for glucose is low and the excretion of sugar is disproportionately high It is, therefore, often difficult to prevent patients from developing either ketoacidosis or severe insulin hypoglycemia We have favored the use of one of the intermediate acting insulins, Lente or NPH or Globin insulin mixed with regular insulin In the third trimester we often supplement with regular insulin before lunch, before supper and even at bedtime The caloric prescription obviously must be adequate We plan 30 calories per kilogram of increasing body weight, but at the same time try to maintain the weight gain to below 15 pounds so that in the third trimester the patient may receive a caloric prescription below that of the first trimester The carbohydrate should be fairly liberal, 180-250 grams (it has been estimated that the fetus metabolizes 50 grams of glucose in the third trimester) the protein high, up to 2 grams per kilogram, and the fat merely to complete the caloric prescription

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SALT FREE—see list of salt-free foods

HORMONE SCHEDULE DATES	Prog (mg)	Stil (mg)	Stil & Prog Mix (mg)	Stil Tablets (mg)	Prog Tablets (mg)	Total cc	Total No Tablets	
							Stil	Prog
to								
to								
to								
to								
to								
to								

SPECIAL DIRECTIONS

Take am hlor thyro d and un caps daily iron when instructed
Check measurement and dosage hormones periodically

Diabetic Diet for Pregnancy

Name

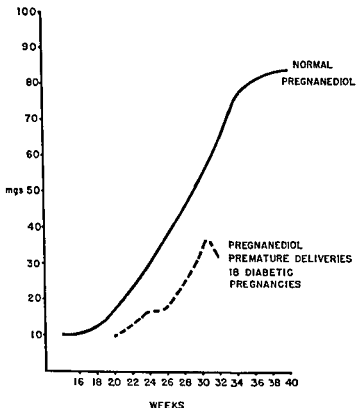
Date

	Breakfast — Crys Insulin ____ Units; NPH Insulin ____ Units		Dinner — Crys Insulin ____ Units		Supper — Crys Insulin ____ Units		Total Daily Diet — C 100, P 105 – F 100 – Cal [illegible] Approximately
	Grams	Portions	Grams	Portions	Grams	Portions	Grams
Eggs		1					
Meat cooked			90	3 oz	120	4 oz	
Bacon							
3% Veg			150	1 cup	150	1 cup	
6% Veg			75	½ cup	75	½ cup	
Oat dry	15						
Oat., cooked	120	½ cup					
Uneedas							
Butter	10	2 tsp	10	2 tsp	10	2 tsp	
Cream 20%							
Milk	210	8 oz	240	8 oz	240	8 oz	
Orange	100	Small	150	Medium	150	Medium	
Cheese							
Potato							
Bread	30	1 slice	30	1 slice	30	1 slice	

10 a m Orange juice—100 grams

3 p m Orange juice—100 g

9 p m: 2 Uneedas (unsa... g milk


SPONTANEOUS PREMATURE DELIVERY
18 PREGNANCIES TERMINATING BEFORE WEEK 34
100
90
80
70
60
mgs 50
40
30
20
10
16 18 20 22 24 26 28 30 32 34 36 38 40
WEEKS
NORMAL
PREGNANEDIOL
PREGNANEDIOL
PREMATURE DELIVERIES
18 DIABETIC
PREGNANCIES

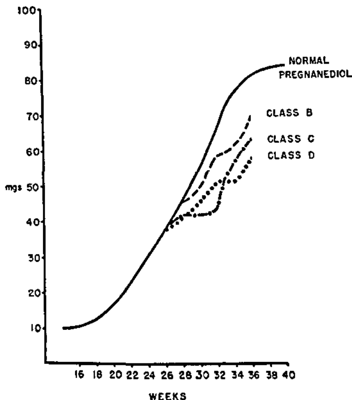
Change of insulin

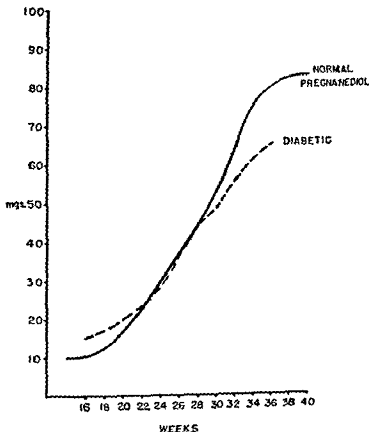
If *pre breakfast test* is poor, increase NPH insulin by 4 units, if test is constantly perfect reduce 4 units

If *pre lunch test* is poor, mix 4 more units of crystalline with NPH, if test is perfect, reduce crystalline insulin

If the *pre breakfast test* is poor, and the *pre supper test* perfect, add 4 units of NPH insulin at bedtime, and increase the dosage to make the rising test sugar free

The use of female sex hormones is the most controversial part of our management It is our contention that an imbalance of female sex hormones characterizes abnormal pregnancy in the diabetic woman, that this abnormality consisting of a high level for serum chorionic gonadotrophin between the 24th and 36th week, low levels for serum estrogen and low excretion for pregnanediol precedes and thereby predicts abnormal course and fetal mortality We contend also that the characteristic imbalance occurs more often where vascular damage is present We contend further that the use of female sex hormones corrects the imbalance, that the correction is followed by increased vascularity, a more nearly normal obstetric course and a higher fetal salvage The use of female sex hormones produces a normal placenta for the period of gestation Finally, with the exception of islet hyperplasia the infant does not show those histological characteristics which were formally described as specific for the infant of the diabetic mother Our data, based upon median values for excretion of pregnanediol, support the thesis that the imbalance of female sex hormone characterizes abnormal pregnancy and poor outcome The most abnormal curve was found in those patients where the delivery occurred spontaneously prior to week 34 (Chart I) An almost equally abnormal curve was found in the patients who had toxemia (Chart II) and a slightly less abnormal curve in those patients with nonsurviving infants (Chart III) When the obstetrical course was normal and the infant survived, the curve was normal (Chart IV) The suggestion that the progression of vascu-


PREGNANEDIOL EXCRETION DIABETIC
PREGNANCIES BY CLASS COMPARED
WITH THE NORMAL
100
90
80
70
60
mgs 50
40
30
20
10
16 18 20 22 24 26 28 30 32 34 36 38 40
WEEKS
NORMAL
PREGNANEDIOL
CLASS B
CLASS C
CLASS D


LIVE BORN AND SURVIVING INFANTS
PREGNANCIES UNCOMPLICATED WITH
PREMATURE DELIVERY (BEFORE WEEK 34)
OR WITH TOXEMIA
173 CASES
100
90
80
70
60
mgs.50
40
30
20
10
NORMAL
PREGNANEDIOL
DIABETIC
16 18 20 22 24 26 28 30 32 34 36 38 40
WEEKS

The parenteral route is selected to insure absorption and to avoid rapid conjugation In addition to the alteration of the dose by chemical findings, any one of the following suggests a need for the increase in dosage of therapy signs of toxemia, rapid gain in weight, demonstrable edema and/or hydramnios, and irritability of the uterus manifested by Braxton Hicks contractions

The comparative results of our patients receiving and not receiving hormonal therapy were as follows From January 1, 1936 to February 26, 1956, 864 cases had determination for one or more of the female sex hormones of pregnancy These reported cases reached week 28 The fetal mortality in 154 cases receiving no female sex endocrine therapy was 32 per cent, whereas the fetal mortality in 710 cases receiving sex endocrine therapy was 12 per cent The total fetal and infant loss by class is shown in Table 26 Classes A and B compare favorably with the expected normal of 87 per cent In addition to the more favorable course, the higher fetal survival, the normal placenta and the more nearly normal histology found in these children of diabetic mothers receiving female sex endocrine therapy, certain other side reactions have been observed The incidence of toxemia has fallen to 3 per cent. The protection of the retina is shown by the failure of the retinopathies to progress or be precipitated in adequately treated cases, the number of hemorrhages sometimes being fewer at the end of pregnancy than they were at the start, and the even more dramatic suggestion, that of lowering of insulin requirement Thus, among those patients whose diabetes started in childhood, where a stable adult dose had been established, it was found that 60 per cent required appreciably less insulin after pregnancy and this treatment than they had before, in 50 per cent the decrease amounted to 50 per cent and in 20 per cent to 75 per cent Some of these patients have been followed for as long as 10 years Subsequently to the pregnancy one patient so treated

lar damage favors the hormonal imbalance (Chart V) was shown by the median pregnanediol curves by classes The most markedly abnormal curve is found in Class D, characterized by early vascular lesions We have presented and published data which appear to indicate that when therapy is administered but the imbalance is not corrected that the obstetric course is as abnormal as when no therapy is given. The fetal mortality also remains high when therapy is given but the imbalance not corrected, but falls when the imbalance is corrected

The schedule for parenteral hormonal therapy is, therefore, given to the patient at first visit and is as follows Class A, unless there is some special indication by history, receives no therapy, Classes B and C, a daily intramuscular injection of stilbesterol and progesterone starting with 25 mg and reaching at least 125 mg, Classes D, E, and F start with 25 mg and receive at least 200 mg The indications for increase in therapy include failure of the chorionic gonadotrophin to fall between the 24th and 36th week and failure of the abnormally low pregnanediol excretion to rise to at least the minimum level of the curve of Venning and Browne The most recent schedule which has been used in our patients is shown in Table 23

TABLE 23

DAILY INTRAMUSCULAR DOSAGE OF STILBESTROL AND PROGESTERONE (IN MG)

	Class				
Week of Pregnancy	*B*	*C*	*D*	*E*	*F*
0-16	25	25	25	25	25
17 19	25	25	50	50	50
20-23	50	50	100	100	100
24-29	100	100	125	125	125
30-33	100	100	150	150	150
34 to end	125	125	200	200-250	200-250

(Cost to patient $50 to $125)

BREAD AND ITS EXCHANGES You should eat only *low sodium* bread Below is a list of exchanges for *one average slice of salt free bread*

½ cup cooked plain rice ½ cup cooked spaghetti noodles, macaroni one small white potato for baking or boiling ½ cup white mashed, one piece unsalted Matzoh, ¼ cup *fresh* lima beans, ½ cup cooked cereal, ¾ cup Puffed Rice or Puffed Wheat, ⅔ biscuit Shredded Wheat, one small ear sweet fresh corn or ½ cup frozen corn

DO NOT USE the following Regular bread, "quick-cooking" cereals, dry cereals not listed, self rising flour, salted popcorn, salted crackers, potato chips salted nuts, pretzels

MILK, EGGS AND BEVERAGES You may use milk as a drink, in soups in combination dishes and with coffee or tea Use fresh or evaporated milk unless low sodium milk has been prescribed

OMIT THESE FOODS cheese, cream, sour cream, ice cream, packaged puddings

MEAT, FISH AND POULTRY You may choose from many kinds This list tells you how large a *three ounce* (3 oz) serving of lean, boneless meat is

LEAN BEEF	Hamburger—1 large patty Roast—2 slices, 4 in by 4 in by ¼ in , Stew—½ cup meat, Steak—one small
LAMB	Roast—2 slices, 3 in by 3 in by ½ in., Chops—2 rib or 1 kidney Stew—½ cup meat
CHICKEN	½ small broiler, Roast—3 slices 3 in by 3 in by ¼ in , One leg and one slice, 3 in by 3 in by ¼ in
LIVER	2 slices, 3 in by 3 in by ¼ in
PORK	Chop—1 large, Roast—1 slice, 3 in by 3 in. by ¼ in
VEAL	Chop—1 medium, about ½ in thick, Roast—1 slice, 3 in by 3 in by ¼ in
TURKEY	Roast—2 slices, 4 in by 3 in by ¼ in
FISH	1 slice 3 in by 3 in by 1 in thick of fresh halibut, fresh cod, fresh salmon fresh perch, fresh bass, fresh trout, fresh oysters (12 to 15 "Dietetic" tuna—¾ cup (water packed and low sodium)

OMIT any meat, fish or poultry that is smoked brine cured, canned, salted dried, or salted and soaked (kosher) This includes cold cuts, bacon, ham, and sausage Do not eat canned soup *of any kind Home* made soup is all right if you use no salt or meat extracts

TABLE 24

FETAL AND INFANT SURVIVAL BY CLASS FOR ENTIRE PERIOD OF PREGNANCY TREATED WITH AND WITHOUT FEMALE SEXOGEN

	No Female Sexogen (278) 1936-1950		*Female Sexogen (289) 1950-1954*	
	Number of Cases	*Per Cent Survival*	*Number of Cases*	*Per Cent Survival*
A	21	100	5	100
B	97	67	66	87
C	83	48	80	80
D	45	32	103	74
E	19	13	22	84
F	13	—	13	46

showed hypertrophy and hyperplasia of the islands of Langerhans in the 15th year of diabetes at age 23 years Only 5 per cent of cases treated without female sexogens showed reduction of insulin dose

Certain measures have been found helpful in the prevention and correction of edema and to a lesser extent hydramnios The low sodium diet of 1 gram is one A low sodium list is given to these patients at the start of pregnancy In addition, each receives one gram of ammonium chloride four times daily and a diet high in protein, 2 grams per kilogram of body weight If these measures fail in the third trimester when hydramnios is a more important complication, mercurials in small doses may be administered, namely, 2 cc of mercuhydrin once or twice a week or 1 cc of Theomerin three times weekly When medical measures have failed completely, transabdominal amniotomy, planned about two weeks before expected delivery date, has been found to be of value

PRESCRIPTION OF LOW SODIUM DIET TO BE GIVEN TO THE PATIENT

The most important feature of this diet is that the amount of sodium is extremely low The major source of sodium for the average person is common salt (SODIUM CHLORIDE) Do not use foods made with salt or sodium (Na' is a symbol for sodium) Read the labels on all canned, frozen, and packaged foods

The timing of the delivery is of greatest importance The Class A patients, sub clinical diabetics are carried to term and we expect that the majority of these patients will be delivered normally By the method of trial and error, our Class B and C patients are carried, if possible to the end of week 37 Our D s, E s and F s the vascular group, are re-evaluated at the end of week 35 If the infant appears small and the case uncomplicated, then an effort is made to carry the pregnancy longer The choice of delivery is the obstetrician's More and more often our patients are given a trial of labor Induction has usually been attempted with rupture of the membranes in favorable cases, in those which are not so favorable priming with Pitocin and then when the cervix is satisfactory, rupture of membranes An 8 hour trial of labor is given If the patient has not progressed satisfactorily by this time, then Caesarean section may be done The short term case with a large infant is more apt to require surgical delivery than is the long term patient where the infant is frequently small and short satisfactory labor may be anticipated In 1955 half of our patients were delivered normally

In timed deliveries the patient receives no long acting insulin for about 24 hours prior to the scheduled time for delivery If labor is induced in the morning we usually give half the usual dose of the long acting insulin and then supplement it immediately after delivery Whether the delivery is pelvic or abdominal glucose is administered during the actual delivery and during the times for the peak action of insulin Sedation is kept to minimal levels and the actual delivery done either under spinal or epidural anesthesia In the post partum period insulin is usually decreased to the pre pregnancy dose levels

The care of the infant in the immediate post natal period is of greatest importance The following conditions have been given as responsible for poor behavior in these infants when it occurs (1) Hypoglycemia due to hyperinsulinism

RICE HAMBURGER AND TOMATO CASSEROLE

3 ounces hamburger
¼ cup cooked rice
½ medium tomato
1 tsp sweetener
½ tsp chopped onion
½ tsp chopped pepper or other allowed spices

Place onion green pepper and hamburger in dry frying pan and brown slightly Add *peeled sliced* tomatoes Cook partially Add rice and cook until tomatoes are tender Add sweetener and cook one minute One serving

TOMATO SOUP

one teaspoon low sodium butter
1 teaspoon flour
⅓ cup strained fresh stewed tomatoes
¼ cup milk

Melt low sodium butter in top of double boiler Add flour and mix thoroughly Add milk slowly and blend with strained tomatoes Mix well

LOW SODIUM FRENCH DRESSING

⅓ cup vinegar
⅔ *cup salad oil*
¼ teaspoon dry mustard
⅛ teaspoon pepper
1 teaspoon strained fresh tomato pulp if desired
⅛ teaspoon paprika
1 teaspoon finely chopped onion

Mix ingredients and shake well before using

CUSTARD

1 egg
½ cup milk
1 tablespoon sweetener
⅛ *teaspoon* cinnamon
½ teaspoon vanilla

Beat egg slightly Add sugar cinnamon and vanilla Blend well add milk and beat thoroughly Place in container and set in pan of warm water Preheat oven and bake at 325 degrees for 40 minutes Makes 2 servings

GELATIN FOUNDATION FOR FRUIT SALADS

2 tsp gelatin
3 tablespoons cold water
¼ cup boiling water or fruit juice
sweetener
1 tablespoon lemon juice
¼ cup drained fruit

Soak gelatin in cold water Dissolve it in ¼ cup boiling water or fruit juice Add sweetener and lemon juice Chill and when about set add fruit 2 servings

MEAT SAUCE

2 tablespoons olive oil
1½ tbsp chopped onions
3 ounces ground steak paprika parsley dried basil or thyme
½ cup fresh cooked tomatoes
2 tablespoons water

Brown onion and meat Add remaining Simmer two hours

The timing of the delivery is of greatest importance The Class A patients, sub-clinical diabetics are carried to term and we expect that the majority of these patients will be delivered normally By the method of trial and error, our Class B and C patients are carried, if possible, to the end of week 37 Our D s, E's and F's, the vascular group, are re-evaluated at the end of week 35 If the infant appears small and the case uncomplicated, then an effort is made to carry the pregnancy longer The choice of delivery is the obstetrician's More and more often our patients are given a trial of labor Induction has usually been attempted with rupture of the membranes in favorable cases, in those which are not so favorable priming with Pitocin and then when the cervix is satisfactory, rupture of membranes An 8 hour trial of labor is given If the patient has not progressed satisfactorily by this time, then Caesarean section may be done The short term case with a large infant is more apt to require surgical delivery than is the long term patient where the infant is frequently small and short satisfactory labor may be anticipated In 1955 half of our patients were delivered normally

In timed deliveries the patient receives no long-acting insulin for about 24 hours prior to the scheduled time for delivery If labor is induced in the morning we usually give half the usual dose of the long-acting insulin and then supplement it immediately after delivery Whether the delivery is pelvic or abdominal glucose is administered during the actual delivery and during the times for the peak action of insulin Sedation is kept to minimal levels and the actual delivery done either under spinal or epidural anesthesia In the post partum period insulin is usually decreased to the pre pregnancy dose levels

The care of the infant in the immediate post natal period is of greatest importance The following conditions have been given as responsible for poor behavior in these infants when it occurs. (1) Hypoglycemia due to hyperinsulinism

(2) Primary pneumonia (3) Congestive heart failure (4) Cushing's syndrome (5) Respiratory acidosis (6) Hypoxia (7) Pulmonary hyaline membranes with atelectasis Some of these conditions obviously overlap Today's evidence throws disfavor upon the concept of hypoglycemia due to hyperinsulinism because the blood sugar of the normal infant, especially the premature infant, varies from 30-60 mg These infants show values very little, if any, below those of infants whose mothers do not have diabetes Glucose is not administered *routinely* but actually *avoided* because of their tendency toward edema Primary pneumonia does not appear to be an important cause of poor behavior but may complicate the hyaline membrane syndrome, so prophylactically chemotherapy and antibiotics are usually employed These infants certainly do resemble individuals with Cushing's disease but that does not appear to be an adequate explanation for their respiratory difficulty It may explain their tendency toward easy hemorrhage Their excretion for 17 ketosteroids and 17 hydroxysteroids exceeds that of other infants Congestive heart failure has been suggested by the large heart, large liver and large spleen so that such infants have been digitalized in many nurseries

Our explanation of the respiratory difficulty is hypoxia with hyaline membranes The management we employ to prevent this complication is aspiration of the stomach and upper air passages for removal of the amniotic fluid as a contributing cause, dehydration to correct pulmonary edema The use of dry oxygen, air and moist oxygen is being evaluated at the present time, but more and more evidence seems to indicate that oxygen of low content is more desirable than an atmosphere of high content

The incidence of clinical and chemical diabetes in the offspring of diabetic mothers and of young diabetic *fathers* in our experience has been comparable, 23 and 21 per cent respectively The expected incidence of diabetes in the population when one parent is diabetic is 22 per cent entire

life span of the individual Although we believe that the islets of the infant should be protected by careful chemical control of diabetes, we believe that the development of diabetes subsequently is on a genetic basis, that early diagnosis must be stressed with random blood and urine tests up to age 5 and a yearly glucose tolerance test thereafter If the tolerance test appears abnormal, then under stress conditions such as rapid rates of linear growth, fever, emotional disturbances in later life, pregnancy, menopause or if obesity complicates, then a regulated diet with or without small doses of insulin during the acute stress situation may be employed prophylactically

Results The maternal case survival is 99 7 per cent Maternal survival can be assured, and possible lessening of insulin requirement occurs Prevention of the precipitation and progression of retinopathies appears to have followed the present program

The programs for diabetes prevention for the child have been but recently established

The early fetal loss is now comparable to that of the general population, namely, 10 per cent The fetal and infant loss in patients not receiving female sex hormones is 32 per cent, for those receiving them, 12 per cent If cases with retinopathies are excluded, the viable fetal and infant loss is 9 per cent (For further details see Chapter XIX on Children Born to Diabetic Mothers)

Summary of the Management of the Diabetic Obstetrical Patient

First Visit of New Patient

Histories

- Medical Diabetic
- Past Obstetrical History

First Obstetrical Visit of Diabetic Previously Seen

- Past Dietary and Insulin Treatment
- Symptoms of Diabetic Activity
- Estimate of Diabetes Control

Major Diabetic Complications in Past
- a Infection
- b Neuropathy
- c Vascular Disturbances
- d Ketoacidosis

Laboratory Determinations at Visit

Blood Sugar
Wasserman
Non Protein Nitrogen
Hemoglobin
White blood count
Chorionic Gonadotrophin (quantitative)
Rh factor
Complete urinalysis with quantitative albumin
Urea clearance
Phenosulfonphtalein

X ray Studies

Chest
Legs
Lateral aorta
Pelvis

Electrocardiogram
Ophthalmoscopic consultation if indicated

Classification of Patient for Fetal Hazard

Class A Glucose tolerance test slightly abnormal
Class B Duration of DM under 10 yrs, onset over 20 yrs, no vascular complications
Class C Duration of DM 10 to 19 yrs, onset at 10 to 19 yrs, no vascular complications
Class D Duration of DM over 20 yrs onset at less than 10 yrs, calcification in legs, retinitis
Class E Calcified pelvic arteries
Class F Nephritis

Management

Diet Obstetrical diabetic diet *Plan to hold gain in weight at 15 pounds*
Low sodium list
Emergency lists for nausea, fever, diarrhea
Insulin *Basic and supplementary*
Emergency plan for fever
Teach acetone test
Record sheet for home tests and acetone and sugar

Prescriptions for ammonium chloride, thyroid, polyvitamins, iron (if indicated)
Female sex hormone schedule (see dose schedule). Husbands taught to administer injections
Simple summary describing course of pregnancy in diabetes

Special Laboratory

Chorionic gonadotrophin prepared Tuesday, read and recorded Mondays
Pregnanediols reported on third day

Weekly visit

Weight
Blood sample for sugar, NPN, hemoglobin, quant chorionic gonadotrophin
Single urine specimen for complete analysis
24 hour specimen collected Monday for pregnanediol, quantitative sugar, acetone, quantitative albumin
Instruction hormone change at visit, insulin change by *telephone in 24 hr, diet at visit,* ammonium chloride, ferrous sulphate

Physical Examination

Blood pressure
Heart and lungs
Retina
Inspection for edema
Inspection of sites of injection of sexogens
Height of fundus
Evidence of hydramnios
Fetal heart

Interval History

Diet for past 24 *hours*
Reactions to insulin
Tests
Symptoms of diabetes
General health, infections etc
Bleeding
Contractions
Nausea Vomiting

Treatment Mercurials after 30 weeks if hydramnios present

Pre-Delivery Hospitalization

Physical examination
Daily weight

Daily quantitative sugar and albumin, acetone
Complete blood count
Urinalysis
Blood Sugar Fasting 11 a m—4 p m. (once or twice weekly)
Weekly chorionic gonodotropin electrolytes
Bi weekly Sodium pregnandiol glucoronidato

Treatment
Daily change in insulin
Weekly change in female sex hormones

Day before delivery

Omit supplementary insulin

Delivery Day

No insulin pre operatively
½ to ⅔ dose of insulin post operatively
1000 cc 10% glucose pre operatively and in late afternoon
Diet 50 grams carbohydrate orally
Insulin Supplementary by test

Second Day

Diet Carbohydrate 150 grams Protein 50 grams Fat 50 grams 1000 cc 5% glucose
Insulin Basic and supplementary by tests

Third Day

Diet Carbohydrate 180 grams Discharge Diet maintenance 30 calories per kilo C 200 protein 2 grams per kilo and fat to make up caloric intake Protein 60 grams Fat 60 grams
Insulin Basic

Fourth Day

Diet Final
Insulin Basic

CHAPTER XVIII

MANAGEMENT OF JUVENILE DIABETES

In this thirty-third year of the insulin era, it has become apparent that the problems of growth and development in juvenile diabetes have largely resolved themselves, that certain etiological factors appear to be well established and programs for prevention in susceptible individuals are suggested That the juvenile form of diabetes follows a natural course is recognized by those who see many of these patients *From this knowledge logical rules for management* may be formulated Successful methods for prevention and treatment of all except one of the four major classes of complications—ketoacidosis, sepsis, tuberculosis—are available and new data concerning the mechanisms of this one, vascular damage, are being assembled Based upon past treatment alone, the expectation of life in juvenile diabetes is nearly two thirds of the normal span Already 1032 of the 3732 Joslin Clinic childhood diabetics have survived twenty or more years of their disease Diabetic nephropathy (preventable diabetic nephropathy) has replaced other chief causes of death, accounting for nearly three fifths of their total mortality Finally, programs for altering the course of juvenile diabetes are not only contemplated but are actually progress

Juvenile Diabetes

The term juvenile diabetes is used here to designate all those patients whose diabetes onset has occurred under the age of 15, and the designation of juvenile type diabetes is continued throughout their life span Juvenile diabetes is not a common form of the disorder Some 5 per cent of all diabetics have onset of their disease in these childhood years Diabetes is also not a common disorder in childhood for only 1 child out of every 2500 contracts the disease under the age of 15, yet the number of juvenile diabetics surviving in the United States is appreciable We estimate that there are some 100,000 such individuals in our country today

Incidence of Juvenile Diabetes

Three peaks in the age of onset of diabetes occur in childhood These are at 3, 6 and 12 and coincide with periods of a slow rate of pancreatic islet growth Unlike experience with older patients the sex distribution in childhood is even Girls coincidental with their earlier maturity have their peak of onset at age 11 and boys at age 13

TABLE 25

Incidence of Juvenile Diabetes

Total	*Per Cent*	*No*
Among Diabetics	5	
Among Children	0 004	
Total in U S Surviving Childhood Diabetes		100 000
Sex—Equal		
Age—Peaks at age 3 6 and 12		

Etiology and Programs for Prevention

Because of the many opportunities for re checking family histories the importance of the rôle of heredity in diabetes is revealed constantly in the juvenile form of diabetes

When first seen, positive family histories are found in but 20 per cent of the cases, at twenty years' duration, in 60 per cent

The overall evidence favoring the genetic origin of the diabetic tendency is shown in the concordant development of diabetes in similar twin mates and the statistically significant difference between the incidence of diabetes in the parents and siblings of diabetics and control populations In fifty per cent of the Joslin Clinic similar twin patients both of the pair had contracted diabetes and diabetes was found seven times more often in parents and siblings of diabetics than in the non-diabetic control population studied

The transmission through recessive genes has been shown in case histories analyzed statistically in families tested with glucose tolerance tests, and in analyses of pedigrees providing corrections are made for the peculiar age behavior of diabetes and the chances of dying prior to the clinical recognition of the disease

The most important diabetes precipitating factors in childhood appear to be linear growth and puberty Of less frequency are infections, stress and clinical disorders of hyperactivity of the pituitary, adrenal and thyroid

TABLE 26

ETIOLOGY

Primary Inherited Tendency

Overall Data	*Recessive Genes*
Similar twins concordantly (50 per cent)	Analysis by case histories
Incidence in {Parents, Siblings} 7x controls	by tested families
	by pedigrees

Secondary Precipitants

Linear growth
Puberty
Stress
Infection
Hyperactivity {Thyroid, Pituitary, Adrenal}

The protection of susceptible individuals by dietary regulation and by insulin during these critical episodes is not unfeasible Hoet, using the pregnant latent diabetic has already initiated a preventive program On a genetic basis Steinberg had predicted maximum susceptibility Thus, maximum susceptibility occurs when both parents are diabetic, and *is nearly as great, 80* per cent, when one parent and grandparent and sibling of the parent on the other side have revealed diabetes The susceptibility is 61 per cent when parent and other parents sibling or grandparent on that side have diabetes With sibling and one parent, 50 per cent, parent and first cousin on the other side 42 per cent, one grandparent on both sides 37 per cent, two grandparents, spouses, 22 per cent, one parent, 22 per cent, one grandparent 14 per cent, and first cousin 9 per cent

TABLE 27

GENETIC PREDICTABILITY OF DIABETES (Maximum)

		Per Cent
Parent + grandparent of other side and that parent s sibling		80
Parent and sibling of other parent		61
Parent and grandparent of other side		61
Parent and 1st cousin on other side		42
One grandparent on both sides		37
Two grandparents—spouses		22
One parent		22
One grandparent		14
First cousin		9
Both parents = 100		
	Mendelian cross	
Sibling—depends upon	MM x MM	100
	MM x MM	50
	MM x MM	25

Diagnosis

The criteria for the diagnosis of diabetes in childhood are *the same as in the adult patient namely,* the demonstration of hyperglycemia and glycosuria Because glycosuria occurs almost universally in children under certain circumstances

one finds that children are placed upon a diabetic routine before the diagnosis is established Therefore, in subclinical cases it is important to establish the diagnosis accurately Preparation of the patient for a glucose tolerance test is important The patient should be afebrile, not having received a restricted diet or insulin or glucose for the week prior to the test In the prescription of glucose for the child, age and size affect utilization Thus, under age 3 the child normally tolerates 3 grams of glucose per kilogram of body weight, above the age of 3, 1 8 grams of glucose per kilogram of body weight, but it is simpler and easier to remember 1 gram per pound The diagnosis is made when there is glycosuria and when the fasting blood sugar, venous, rises to 130 mg, the postprandial venous blood to 170 mg or postprandial capillary blood sugar to 200 mg The classification of melliturias is the same for children as it is for adults Galactosuria occurs commonly in malnourished infants and lactosuria in the nursling

Natural Course of Diabetes in Childhood

Typically, the onset of diabetes in childhood is acute and the early course virulent so that the first recognition may be made during severe ketoacidosis In spite of this characteristic type of onset and early course, within some few months of the time in which treatment is inaugurated the character of diabetes changes to one of great mildness Insulin requirement falls to spectacularly low levels and a phase of remission is established Its duration is of variable lengths, from several months to several years

Intensification of diabetes appears to be associated with linear growth, puberty, ketoacidosis, hypoglycemia, poor control, stress and infection This intensification is so great in degree that by the third to the fifth year of the duration of diabetes a near total or total diabetic state is reached The evidence which favors this concept is clinical, chemical and pathological Clinical evidence of the progression of the

juvenile diabetes is shown by the development of nocturnal hyperglycemia, somewhat masked by today's use of longer acting insulins Wrenshall has found little or no extractable insulin in the juvenile diabetic pancreas in contrast to 50 to 75 per cent of the normal quantity extracted from the pancreas of diabetics whose disease commenced after the completion of growth and development The assays for insulin in the blood made by Bornstein revealed no assayable insulin in juvenile type diabetes in contrast to varying amounts in the blood of diabetic adults With special stains Bell found no evidence of insulin in the islets of *juveniles* in contrast to adults and in long term juvenile diabetes Warren has reported the pancreas to be small with few islets

The restoration of normal carbohydrate metabolism, of normal synthesis of protein and of fat, the maintenance of hormonal balance among those hormones concerned with carbohydrate metabolism becomes difficult because patients, totally diabetic, are completely dependent upon exogenous insulin which is unaffected by tissue sugar level Juvenile patients, therefore, constantly exhibit periods of insulin excess and of insulin lack

Management of Juvenile Diabetes

Logical rules for management are suggested by this characteristic course

From these foregoing statements it is evident that all diabetic children with the clinical symptoms of the disorder should receive insulin continuously from the day of recognition of the disease Two standards are used for the initial prescription, one based upon age and the other upon weight *Based upon age—at year 1, 5 units, at age 5,* 10 units, at age 10, 20 units and at age 15, 30 units or ½ unit of insulin per pound of body weight All types of insulin can be used successfully in the management of the juvenile patient, but as

TABLE 28

INSULIN MANAGEMENT

All childhood diabetics should receive insulin

Initial Dose—

By Age =	Years	1	5	10	15
	Units	5	10	20	30
By Weight =	½ unit per kg body weight				

Type—

INTERMEDIATE	PER CENT CASES
Alone	10
Mixed with quick in single dose	65
Divided doses A.M. and P.M.	25

Regulation by urine analyses

Pre-Breakfast	Pre-Supper—Intermediate
Pre-Lunch	—Quick
Second of two voided specimens desirable	

convenience of administration favors correct and continuous use, intermediate and long acting insulins are to be favored over the short and quick acting varieties Thus, in the period when regular insulin alone was available it was necessary to use four daily injections of insulin to bring about adequate control Globin insulin, excellent in adults does not appear to have 24 hour action in children It may be supplemented with crystalline before breakfast or lunch with globin insulin administered before the evening meal or may be given in two daily injections About 10 per cent of the children, usually the short term cases, are treated successfully with NPH alone, 65 per cent with a morning mixture of regular and NPH, an additional 25 per cent require the administration of a pre-supper or bedtime dose of NPH American Lente insulin has been designed to have the same time action curve as NPH and for this reason the frequency of injection is essentially the same Protamine zinc insulin alone was not satisfactory for the juvenile patient We favored separate injections of regular and protamine In

the ratio of regular to protamine as a separate injection was frequently 3 1, at age 5 the requirement was usually equal, 1 1 and older children would usually require as a separate injection 1 unit of crystalline for 2 of protamine A 3 1 *mixture* of regular and protamine is utilized as 1 1 and a 2 1 mixture of regular and protamine is utilized as a 1 2

The regulation which we find helpful is based upon the pre meal test, the second of two voided specimens being a spot test, indicating more closely the metabolic state of the body at the moment With the single timed injection of intermediate or long acting insulins, the pre-breakfast test becomes the guide for increasing or decreasing these varieties, whereas the pre-lunch test is the best guide for increasing or decreasing quick acting insulins

A mathematical rule for the regulation of insulin has been recommended by Hartmann and is calculated as follows The total glucose of the diet is estimated From this is subtracted the quantity of glucose which was excreted in 24 hours When this figure is divided by the dose of insulin received, one can determine how much glucose 1 unit of insulin utilized in this particular patient and then the deficit supplied

Because the child develops hypoglycemia easily when rendered sugar free and accumulates sugar rapidly when not, daily changes are recommended when indicated If the second dose of intermediate acting insulin is required, the pre breakfast test becomes the guide for the bedtime dose of intermediate acting insulin, the pre-lunch test remains the guide for the regular insulin and the pre-supper test becomes the guide for the morning dose of intermediate acting insulin On days of fever the basic dose of insulin should be continued and supplemented with rapidly acting insulin, in 4-8-12 unit doses at 3-4 hour intervals

The compl[illegible] in the child are essentiall[illegible] Because of the

child's activity and the small reserve of glycogen in the smaller muscles and liver, hypoglycemia occurs much more frequently than it does in the adult patient Insulin atrophy, too, occurs much more frequently in juvenile than in adult patients One would expect because of the tendency of the child to administer insulin in a single area that one would see more areas of induration Allergic manifestations occur less frequently in the child, perhaps due to the fact that in most instances the insulin is administered continuously Local urticaria at the start of treatment, however is extremely common Because of greater chances for errors in aseptic technique, abscesses occur more frequently in the child than in the adult patient Edema is not uncommon nor is presbyopia Resistance to insulin, however, has been observed very infrequently in the juvenile group

Dietary Treatment of the Juvenile Patient

One of several rules may be employed in the plan for the caloric prescription of the juvenile patient A very simple rule is based upon age alone starting with 1000 calories at age 1 and adding 100 calories per each year of age until the completion of growth and development Obesity complicates adolescent diabetes and so at the completion of growth, which is approximately at age 13 for girls, the caloric prescription must be lowered to adult level Another rule based upon weight and age is the following 100 calories per kilogram at age 1 dropping to 80 at age 5, 60 at age 10, and 40 at age 15 Height is another possible basis —35 calories per inch or somewhere between 80-100 per cent above the basal metabolism One convenient way of estimating the basal metabolic rate is by the Wetzel grid For activity all these diets should be increased some 20 per cent

With the common metabolic pathway and the common metabolic pool, the division of the diet into its component

parts—carbohydrate, protein and fat—has lost some of its significance, but it still remains a convenient way to prescribe diets The basis for the prescription of the normal diet is the distribution of carbohydrate, protein and fat in milk which is 50 per cent of the calories in carbohydrate, 15 per cent as protein and 35 per cent as fat Hartmann reverses this prescription, 35 per cent carbohydrate, 15 per cent protein, and 50 per cent fat We have favored 40 per cent of the calories as carbohydrate, 20 per cent as protein and 40 per cent as fat A quick way of calculating the diet is to determine the calories and then 10 per cent of the figures for calories gives the grams of carbohydrate, one-half that figure the grams of protein and also the grams of fat To hasten initial desugarization, the caloric prescription should be some 400 calories below the final growth diet *The division of protein and fat may be in even thirds* and of carbohydrate ⅕ for breakfast and ⅖ at noon and at night From the total carbohydrate 25 grams are subtracted for snacks

The third part of the treatment is of great importance, namely, exercise, the timing of which should be somewhat different from that of the child without diabetes, post-meal exercise being favored over pre-meal exercise periods The explanation for the effect of exercise upon diabetes is that it actually simulates the action of insulin Thus, muscle extracts have been found to accelerate the hexokinase effect and exercise has been found to increase the volume of distribution of certain sugars

Our standards for control are the following The blood glucose should be normal before meals, 70 120 mg, the urine free from ketone bodies, the glycosuria less than 5 per cent of the carbohydrate intake, the cholesterol 230 mg or below and a normal growth achieved

The followup of these patients is extremely important and a new patient may require weekly visits After a year, three monthly visits are desirable for physical *examination*

but a blood sugar determination is still desirable at 4 6 week intervals

Readjustments of treatment are made on the majority of our children at summer camp units where the activity is normal and group psychology is helpful in solving the emotional problems of the children

Psychological Problems

Because of the unusual medical responsibility which the details of treatment, menu planning, chemical testing, ad ministration of therapy hypodermically, because of the stress produced by the sudden development of critical situations, insulin reactions or acidosis, because of their knowledge of the future possibilities, certain faulty attitudes may develop in the parents and these in turn affect the child's adjustment These attitudes are largely of four types over-anxious, over indulgent, perfectionist, or indifferent The over-anxious parent may precipitate anxiety states in the child, dependence or defiance, the overly-indulgent, exploitation, the perfectionist, deception and rebellion, the fourth, indifference, depression, more rarely, rebellion.

Self management when the child is ready should be en couraged as well as diabetic undercentralization The exploration for and the development of aptitudes is important Regular emotional support will help in the solution of their problems Reassurance for normal social, recreational, eco nomic future life should be given repeatedly The anticipa tion of pleasing projects at frequent intervals, such as every three months, is a must for the child with chronic disease Expertness in dietetics is a specific need for the solution of the adolescent's social life as is a substitute for food hunger in the form of extra affection for the very young diabetic child Summer camp programs dispel the feeling of being different and finally the value of group therapy should be explored.

ing that with hypertonic solutions extra and intracellular sodium retention occurs

For electrolyte repair potassium has been used if the blood level falls to 3 milliequivalents, if electrocardiographic changes occur, if gastric dilation persists or if the clinical picture of flaccidity and respiratory failure develops

Sodium lactate, ⅙ molar, is used especially if nephritis complicates ketoacidosis Hartmann uses sodium lactate routinely, 40 90 cc per kilogram and Ringer's solution, 40 cc per kilogram Guest favors bicarbonate, Knowles recommends 3 75 grams of sodium bicarbonate added to 600 cc normal salt solution and 400 cc of distilled water and Butler recommends the multiple hypotonic electrolyte solution of Talbot and Crawford, 3 5 liters per square meter This solution contains per liter Na, 40 mEq, K, 35 5 mEq, chloride, 40 m Eq, lactate, 20 m Eq, phosphorus, 15 m Eq, and glucose 0 80 grams Thorn and Forsham recommend adding 500 cc of ⅙ molar sodium lactate (1 9 per cent) or bicarbonate (1 3 per cent) to each liter of 0 85 per cent sodium chloride solution, and to correct or prevent hypokalemia they suggest that potassium hydrogen phosphate, 2 gm, *potassium dehydrogen phosphate,* 0 4 gm, distilled water to 50 cc should be added to a liter of the solution used

Glucose is used by us only if the level of blood glucose is low since its use favors water intoxication and hypokalemia

Carbohydrate (as orange, oatmeal or milk) 5 grams per hour is given when vomiting is controlled, antibiotics are often necessary

Shock may be treated with levofed and hypochloremic anuria with 10 per cent sodium chloride solution

Unless the patient is in marked shock, gastric lavage should be a routine procedure In spite of restlessness and obvious pain, opiates and sedatives should be avoided During convalescence the first day's diet consists of a soft

solid diet of 150 ± grams of carbohydrate, 90 ± of protein and 60 ± of fat which can be derived from the following foods in grams

Bread 90	Chopped meat 120
Cereal 15	Milk 1000
Eggs 1	Orange 450

and the first day following recovery a mixture of regular and intermediate acting insulin may be used

Differential Diabetic Diagnosis

In the juvenile patient the following must be differentiated from ketoacidosis surgical abdomen coexistent with ketoacidosis, uremia, diphtheria, pneumonia hypoglycemia, salicylic acid poisoning, fractured skull and lead poisoning The complications of convalescence from ketoacidosis include hypoglycemia, rebound into acidosis, anuria, shock, aspiration pneumonia, urinary tract infection, arterial thromboses and infection

Prevention of ketoacidosis should be taught by careful chemical control Thus parents can be taught a quantitative determination of sugar for the 24-hour period daily qualitative tests, spot test for acetone, the daily regulation of insulin, the important rule never to omit insulin on a day of fever, continuous reassurance through followup and stress for the hope for curability of diabetes In other words, "Live today in expectation of the cure for tomorrow"

Prognosis

Among childhood cases of coma, the case recovery was 98 per cent and the patient recovery 97 per cent The were no deaths under age 10, 1 under 15, none since 1 in spite of such extremes of disturbed chemistry as a b sugar of 2200 mg and a carbon dioxide content of 1 per cent

Pyogenic Infections

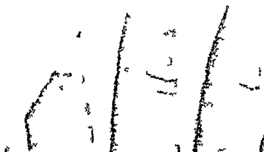
Formerly, up to 1935, pyogenic infections were as lethal in young diabetics as ketoacidosis was prior to 1922 The most frequent infections are those of the skin and of the urinary tract Osteomyelitis, common in adult diabetes is relatively rare in childhood Prior to the discovery of chemotherapy the average duration of life in juvenile diabetics was some seven years, then death from septicemia occurred Perhaps because of difficulty in early diagnosis the especially malignant necrotizing papillitis may even today defy our therapeutic programs and terminate fatally The rules for the management of infections in diabetes are the same as those for the general population However, Staphylococcus albus is more often pathogenic Simple therapeutic rules are as follows penicillin for gram positive, erythromycin for resistant gram positive cocci, gantrisin for gram negative organism streptomycin for resistant gram negative organism, for marked resistance the combination of aureomycin, terramycin and chloromycetin

Tuberculosis

Susceptibility to tuberculosis is great among diabetics The incidence of tuberculosis in juvenile diabetes is ten times that of the general juvenile population Because the tendency to rapid caseation and cavitation characterizes tuberculous infections in this group medical management alone is rarely sufficient so in addition to bed rest SM (streptomycin) PAS and INH segmental resection lobectomy or pneumonectomy have been performed These surgical procedures are well tolerated in young diabetics and the survival has been measurably prolonged

Cataracts

The typical juvenile diabetic cataract may be recognized at the diagnosis of diabetes Many of these do not progress



which diabetes starts is today easily maintained Some children are still treated with forms of rapidly acting insulins alone and the management of diabetic dwarfism remains part of our therapy In addition to adequate calories, adequate protein, adequate vitamins and chemical control, growth promoting substances may be used For girls, thyroid and possibly estrogenic substances, for boys chorionic gonadotrophin or testosterone Interrupted therapy can be prescribed safely over a period of two years The diagnosis of true retardation should be confirmed by x ray examination of the wrists, for if the bone age is normal one is dealing with a physiologically small individual with the probability of normal adolescent spurts of growth

Vascular Damage

Because only one in ten of our juvenile diabetics at 20 years' duration and only one in fifty at 25 years' duration of their diabetes can be certified to be free from vascular damage, the vascular status of these patients is our greatest concern

The evolution of vascular damage in juvenile diabetics is well established Although all types of blood vessels are involved in all forms of vascular damage, the specific disabling and lethal lesions in youth appear to involve capillaries, arterioles and venules, especially those in the retina and in the kidney Although the vessels of the heart, extremities, and brain are not spared, their progression is slow in contrast to the progression in the small vessel group These differences in involvement of the vascular system in diabetes with onset under 15 years of age and in cases with diabetes onset age 15 to 40 are shown in Table 29 Although calcified arteries were nearly comparable in both groups, retinopathy and nephropathy were infrequent in the post-growth onset group In this latter group heart disease was the most common clinical vascular disorder and cerebrovascular accidents and gangrene occurred three and nine times

TABLE 29

VASCULAR CHANGES IN PATIENTS WITH ONSET OF DIABETES IN CHILDHOOD (Under 15 years)

CONTRASTED WITH PATIENTS WITH ONSET AFTER CHILDHOOD (15-40 years)

Age	*Retinopathy Per Cent*	*Nephropathy Per Cent*	*Calcified Arteries Per Cent*	*Coronary Heart Disease Per Cent*	*Cerebrovascular Accidents Per Cent*	*Gangrene Per Cent*
CHILDHOOD CASES (200 Twenty year survivors)						
10-19	2	2	5	0	0	0
20-29	50	20	50	0	0	0
30-39	80	40	78	8	5	2
YOUNG ADULT CASES (200 Twenty year survivors)						
40-49	15	1	75	30	0	0
50-59	23	3	87	43	3	0
60-69	28	7	95	56	13	18

as common respectively as in the childhood group An older age at the time of the study undoubtedly contributed to the frequency of the lesions of the heart, brain and extremities, but the effect of age was not apparent in cases with retinopathy where in the seventh decade their incidence was hardly more than a third for retinopathy and a sixth for nephropathy as it was in childhood cases which had reached the fourth decade

Clinical evidence of vascular lesions is rare under age 20 or under 15 years' duration of diabetes Less than 10 per cent of the juveniles show any clinical form of vascular damage before age 20 and 12 per cent before the 15th year of diabetes (Table 30) The involvement after 20 years is extensive indeed

TABLE 30

DURATION OF JUVENILE DIABETES AND INCIDENCE OF VASCULAR DAMAGE

Duration Years	*Per Cent*
0- 4 9	0
5- 9 9	4
10-14 9	12
15-19.9	50
20-24 9	94
25	98

The order of appearance of the lesions clinically has been retinopathy, calcified arteries, proteinuria, hypertension coronary insufficiency and cerebrovascular accidents

The seriousness, the potentially crippling and lethal character of these vascular lesions is shown by their clinical progression nephropathies almost without fail leading to uremia, retinopathies of the proliferating type to blindness in one quarter of the cases, hypertension to myocardial infarction in one fifth and to cerebral accidents in one tenth *of the cases By contrast, in spite of the incidence of cal*cified arteries, gangrene developed in only two per cent

The search for the cause and the means to prevent vascular lesions has therefore become the main objective in the management of juvenile diabetic patients That extreme degrees of poor control precipitate these vascular lesions all agree, the extreme degree of poor control being ketoacidosis, but that good control protects the patient from vascular damage is a debated point The data of a series of our young long term diabetics evaluated for control and vascular lesions by incidence and intensity has been reported by Keiding Marble and Root One hundred eighty nine cases were evaluated after 20 years of diabetes When control was graded excellent to good (32 cases) grade 3 or 4 retinopathy was found in 3 per cent only, but when it was fair to poor (157 cases) 31 per cent were found to have severe degrees of retinopathy (Table 31A)

TABLE 31A

RETINOPATHY AND CONTROL AFTER 20 YEARS DURATION IN 189 CASES

Control	*No*	*Retinopathy Grades 3 and 4 Per Cent*
Excellent to good	32	3
Fair to poor	157	31

TABLE 31B

NEPHROPATHY AND CONTROL IN 451 CASES OF YOUNG DIABETICS

Control	*No*	*Nephropathy Per Cent*
Excellent	11	0
Good	50	2
Fair	92	17
Poor	298	28

Four hundred fifty-one cases of suitable duration, 10 to 36 years, were graded and evaluated for nephropathy Nephropathy did not occur in the eleven with excellent control, in 2 per cent of those with good control (50 cases), in 17 per cent of 92 cases with fair control but in 28 per cent of 298 cases with poor control (Table 31B) The conditioning of vascular damage by poor chemical control has been reconfirmed in 1954 by Dunlop Using the alternate case study method free diet and no chemical control, restricted diet and chemical control, he found such rapid precipitation and progression of vascular lesions in patients using the free diet and having no chemical control, that he abandoned his experiment Engleson, studying those patients in Sweden in whom this free type of management was first applied, came to similar conclusions

In order to learn more about vascular response and degeneration a study of the small blood vessels at the microscopic level has been made upon our juvenile diabetics by Dr Jorn Ditzel. He selected the conjunctiva as the object of study because this is the only area of the body where arterioles, venules and capillaries can all be visualized in *vivo* One hundred forty children were examined. He found in the vascular pattern of 70 "healthy" children that the *arterioles* entered the conjunctiva parallel to the venules They branched and gave rise to terminal arterioles *Capillaries* branched from arterioles and their network appeared regular and ordered No angulations, tortuosities or local-

ized sacculations were found *Venules* were smooth with an A V ratio of 1 3 to 1 2 There was no extravascular edema or hyalinization The 70 diabetic children studied had had diabetes from six months to thirteen years and their ages at the time of the study ranged from six to eighteen years Three distinct types of patterns were observed In addition to the normal pattern, a group designated as vascular pattern change I and a group complex designated as vascular pattern change II Ten per cent of the children at the time of the examination showed the normal pattern, 81 per cent, vascular pattern change I, and 9 per cent, vascular pattern change II No child whose duration of diabetes was less than 5 years exhibited vascular pattern change II

> The characteristics of vascular pattern change I are arterioles *moderately constricted, venules distended, extravascular* edema and hyalinization and intravascular aggregation of red blood cells The AV ratio is 1 4 to 1 10

> The characteristics of vascular pattern change II are marked arteriolar constriction, capillary closure and venular narrowing The AV ratio is 1 1 perivascular edema and *hyalinization* and intravascular aggregation of red blood cells

The end result of these abnormal reversible vasomotor responses is stasis probably leading to hypoxia and starvation, sequelae which, dependent upon degree and chronicity, will produce degenerative changes

Certain fundamental similarities and differences in conjunctival and retinal vessels clarify possible mechanisms and probable relations to diabetes control The similarities between the conjunctiva and the retina are first anatomical In both tissues the only vessels present are arterioles *capillaries* and venules The responses to stimuli are identical—vascular constriction, dilatation, perivascular edema, hyalinization and intravascular aggregation of red blood cells In both, the rate of blood flow becomes impaired leading to stasis and

finally probably to varying degrees of hypoxia and starvation In contrast to the conjunctival vessels, the retinal vessels have a basement membrane The retinal lymphatic supply is poor whereas lymphatic network of the conjunctiva is rich The metabolic needs of the retina are great, of the conjunctiva, little The capacity for prolonged adaptation in the conjunctiva is high, in the retina, low The conjunctival responses are reversible for a long time, the retinal for a limited time The venous vascular responses are the first and most easily recognized ones in the conjunctiva. These responses cannot be observed in the retina because of the limitation of the magnifying power of the ophthalmoscope Due to differences in functional need, venules are affected in the conjunctiva whereas capillaries and venules both are affected in the retina (Table 32)

TABLE 32

VASCULAR RESPONSE IN CONJUNCTIVAL VESSELS
JUVENILE DIABETES

Pattern I	*Pattern II*
Vascular	Vascular
Arteriolar constriction	Marked arteriolar constriction
Venular distension and darkening color	Capillary closure
A V Ratio 1 [illegible]–1 10	Venular narrowing
Capillary irregularities	
Perivascular	Perivascular
Edema	Edema
Hyaline infiltration	Hyaline infiltration
Intravascular	Intravascular
Aggregation of RBC	Aggregation of RBC

Thus for a long period of time the conjunctival responses are reversible in part or whole whereas the retinal responses may be reconstructed as follows arteriolar constriction, capillary narrowing, venular distension and narrowing leading to aggregation of red blood cells, stasis, hypoxia and

Congestive heart failure requires digitalization, rest and restriction of fluid to 2000 cc

Encephalopathies may require lumbar puncture, magnesium sulphate, hypotensive drugs or anticonvulsants

Exchange resins, splanchnicectomy and rice diets have not been successful in our hands The chronicity of the lesions makes the artificial kidney, replacement transfusions, intestinal or peritoneal lavage useless procedures The use of heparin to alter lipoproteins may be explored further Adrenalectomy—surgical, x-ray or medical, appears too radical.

Survival and Mortality

Of the 3,782 childhood cases seen between 1898 and 1955, 3,031 (81%) are living, 680 (18 5%) have died and 21 (0 5%) are untraced Of 1032 twenty-year survivors, 939 or 91% were living in August of 1955

Nephropathy accounts for nearly three-fifths of all deaths in childhood cases As late as 1943, coma was the most frequent cause of death with infections a close second, nephropathy third, accounting for about 10 per cent of their deaths (page 189), exceeding tuberculosis by 2 per cent Despite nephropathies the prognosis of childhood cases has improved Since 1944 the average age at death has risen to 29 years and duration of diabetes to 19 years, whereas as late as 1943 the average age at death was 19 years and the duration was 10 years The duration of diabetes exceeded 20 years in 40 per cent of the cases dying after 1950 and 6 per cent had had diabetes for more than 30 years

When the prognosis of diabetes is based upon physiological, economic and social results after 20 years' duration, it is excellent, for only 2 per cent of juveniles surviving 20 years' duration failed to achieve adult stature The number attending college exceeds that of the general population Ninety per cent of the employable are gainfully employed and 98 per cent of the offspring of the wives of diabetic males survived the perinatal period Seventy-five per cent of the pregnancies of the females reaching viability survived the peri-

The Clinical Course and Management of Nephropathy

Diabetic nephropathy is a mixed lesion consisting of inter capillary glomerularsclerosis, arteriolarsclerosis, pyelonephritis and arteriosclerosis The clinical picture of nephropathy is revealed by the appearance of proteinuria which is transitory at first, then becomes constant Diabetic retinopathy has usually preceded proteinuria Soon renal retinopathy appears Proteinuria occurs rarely before the fifteenth year of diabetes and rarely before twenty years of age Edema develops gradually as does hypertension which is usually of moderate degree The total protein falls, the A/G ratio is reversed, the cholesterol levels increase and lipoprotein in the SF 12 20 range increases The urine contains doubly refractile bodies but few cells or casts Anemia becomes progressively severe, renal acidosis is common, low salt syndrome develops, congestive heart failure occurs, distressing encephalopathies intervene and uremia is almost inevitable

Prevention Should Be Stressed by Chemical Control

The management of nephropathies must be planned for the phase or phases present

The nephrotic stage is best controlled with diets high in protein, low in sodium The acid ash diet is useful Ammonium chloride and/or potassium chloride or nitrate mercurial or xanthines or magnesium sulphate are indicated amigen, acacia and salt poor albumin may be tried The anemias, largely intractable are benefited temporarily by transfusions of packed red cells, copper, cobalt or iron are usually given a trial

The salt losing phase must be managed carefully Dietary sodium chloride or normal salt solution may be adequate

The acidosis may be treated with sodium lactate if acute and with ammonium citrate if chronic

When uremia develops the sodium may be restricted further to 0 5 daily and protein to 0 5 gram per kilo

large doses of estrogenic substances A sample of seventy-five cases, observed for at least 7 years prior to the pregnancy and for at least seven years after pregnancy were evaluated for changes in insulin requirement Former juvenile diabetics receiving large doses of estrogens in 50 per cent of the cases required less than 50 per cent of their adult stable dose of insulin and 20 per cent required 75 per cent less Only 5 per cent of patients not receiving hormones required less than 50 per cent of their pre-pregnancy dose and none required 75 per cent less These altered requirements have continued as long as 10 years. One patient so treated with estrogen was autopsied at age 23, eight days after delivery, in the fifteenth year of diabetes Extensive islet hypertrophy and hyperplasia were found This observation had not been made before in any of our long term young diabetics For this reason the effect of cortisone in 5 to 15 mg daily doses is being evaluated in some of our juvenile diabetics The period of remission has been chosen for this experiment. In one year some of the cases appear to have responded favorably, but since remissions of the spontaneous type may last up to 3 years, no conclusions can be drawn Thyroxin, 0 1 mg daily, was tried for 6 months but it appeared to intensify diabetes temporarily and its use was abandoned

An optimistic attitude should be held toward the juvenile diabetic patient We have faced the blank wall four times—once when deaths occurred from diabetic coma within two years of the onset, this tragedy was solved with insulin therapy, second, when survival with insulin was possible for some seven years, then death occurred from septicemia—conquered with chemotherapy, antibiotics, and, finally, tuberculosis with its high mortality—conquered with antibiotics, chemotherapy and radical surgery, leaving vascular damage the main problem However, it is possible for juvenile type patients to be free from vascular lesions after 25 years of their disorder and many have minor non incapacitating

natal period One patient was delivered of a normal surviving infant by Cesarean section in the thirty-third year of diabetes, another in her twenty-fourth year of diabetes was delivered through the pelvis of a normal surviving infant Her diabetes was diagnosed at eleven months of age

Attempts to Alter the Course of Diabetes

Because the prognosis for vascular damage in diabetes is serious, students of the disorder are searching for substances which may alter the course of diabetes itself Attempts to alter the course fall into four groups (1) overinsulinization at onset, (2) inhibition of insulinase, (3) pancreatic grafting, and (4) use of islet stimulators Simultaneously, Brush in children and Umber in adults used overinsulinization at recognition of diabetes The rationale was based upon the principle of rest of pancreatic islets, a principle which in experimental diabetes has reversed clinical signs and pathological evidence of the disease Sufficient time has elapsed to show that the trend in diabetes was unaltered The search for the inhibitor of insulinase by Mirsky is based upon the concept that insulin production in diabetes is normal, but that destruction is excessive (Table 33) He believes that BZ-55 (sulfonamid compound) is an insulinase inhibitor

Transplantation of the infant's pancreas to the mother in the advent of neonatal deaths is being attempted (In one patient only has this been done, Case No 11704, age 25, duration of diabetes 23 years, transplant on November 19 1955) The use of islet stimulator substances stems from the experiments of Houssay, Foglia, Rodriguez and Cardeza who have found that estrogen, compound F, cortisone or thyroxin administered within three months of the onset of diabetes in experimental diabetic animals treated with insulin abolished clinical diabetes in six months Pancreatic islets showed marked hypertrophy and hyperplasia That these results could be duplicated in human diabetes was suggested by our experience with pregnancy cases receiving

plaints of nausea, vomiting and abdominal pain Diabetic ketoacidosis must be considered and suspected until it can be ruled out

In addition to the usual physical examination, examination of the eye for the presence of cataract, of the skin for presence of necrobiosis should be made Subsequent examinations are of great value in the estimation of treatment and may reveal signs which indicate the need for change in therapy *Height and weight should be recorded at each visit* Growth and development are of great importance to the child and it is an excellent plan to plot the height and weight upon some standard curve, such as the Wetzel grid or Iowa growth chart Variations in the control of diabetes are often reflected in the growth curve It is of therapeutic value for the child and his family to possess the curve and the duplicate is then kept in the physician's file A measure of therapeutic success is the maintenance of the superior level of growth and development at which the disease starts in the juvenile patients

Inspection of the site of the injection of insulin must be made Children, especially, elect a single area for its administration so that tumefactions develop and from indurated areas the absorption of insulin may be impaired. Areas of atrophy, too, must be sought They occur frequently in both boys and [illegible] lthough they are uncommon in adult men [illegible] smetic importance, and if the identations [illegible] it are [illegible] ed the patient must be in- [illegible] ration those areas which are [illegible] ne prevention and treatment [illegible] unknown

[illegible] is seen rarely in chil [illegible] hus, careful abdominal [illegible] of hepatomegaly and [illegible] is indicated The skin, [illegible] *of xanthosis, as the* [illegible] are highest in caro-

lesions only Of the 64 patients awarded the Victory Medal in the world 27 are juveniles, 14 are patients of the Joslin Clinic, 13 are not Good chemical control characterized these cases There is evidence of the reversibility of vascular responses in diabetes, suggesting programs for the prevention and correction of some of the degenerative changes Decreased severity of diabetes appeared to follow pregnancy and the use of estrogenic substances These experiences compel us to recommend restricted treatment and careful chemical control, admittedly difficult, in order that *the retina and kidney of the juvenile patient may be protected* and that these patients may enjoy useful lives and the promise of discoveries to come

TABLE 33

Attempts to Alter Trend of Diabetes

A Overinsulization	Brush Umber
B Inhibitor of Insulinase	Mirsky
C Graft of Pancreas	Moore Brooks
D Islet Stimulators Estrogen Thyroxin Cortisone Hydrocortisone	

Histories and Physical Examinations of Juvenile Diabetics

To the careful history which is taken on all children additional questions should be emphasized in the history of the diabetic Among these questions is a search for evidence of diabetes in other members of the child s family, for exposure to tuberculosis and for the presence of allergies Of interest from *the point of view of research* is the record of the birth weight of the diabetic child and his siblings and the history of the mother s course during pregnancy Of special importance with these young patients are the com

plaints of nausea, vomiting and abdominal pain Diabetic ketoacidosis must be considered and suspected until it can be ruled out

In addition to the usual physical examination, examination of the eye for the presence of cataract, of the skin for presence of necrobiosis should be made Subsequent examinations are of great value in the estimation of treatment and may reveal signs which indicate the need for change in therapy Height and weight should be recorded at each visit Growth and development are of great importance to the child and it is an excellent plan to plot the height and weight upon some standard curve, such as the Wetzel grid or Iowa growth chart Variations in the control of diabetes are often reflected in the growth curve It is of therapeutic value for the child and his family to possess the curve and the duplicate is then kept in the physician s file A measure of therapeutic success is the maintenance of the superior level of growth and development at which the disease starts in the juvenile patients

Inspection of the site of the injection of insulin must be made Children, especially, elect a single area for its administration so that tumefactions develop and from indurated areas the absorption of insulin may be impaired Areas of atrophy, too, must be sought They occur frequently in both boys and girls, although they are uncommon in adult men The lesion is of cosmetic importance, and if the identations which characterize it are observed the patient must be instructed to select for administration those areas which are of less cosmetic importance The prevention and treatment of insulin atrophy are at present unknown

Although enlargement of the liver is seen rarely in children treated with long acting insulins, careful abdominal palpation should be made for signs of hepatomegaly and change in treatment if it is present is indicated The skin, too should be inspected for evidences of xanthosis as the child elects for vegetables those which are highest in caro-

tene content, namely, the green and yellow pigmented ones

In the juvenile form of diabetes, vascular lesions are almost unknown under the tenth year of the duration of diabetes Clinical evidence of their frequency is rare even under 15 years duration, but examination for these disturbances becomes increasingly important after 5 years Special examinations should include the determination of capillary fragility The technique which is recommended is the use of a tourniquet for 4 minutes at the level of 80 mg of mercury An area 6 cm in diameter is then circled and the petechiae in this area counted A control group of non diabetic young individuals shows that petechiae in excess of 20 in this area should be considered abnormal Careful examination of the retina for the tiny microaneurysm, dilatation of the vein and the dark purple color of the veins is also to be recommended A neurological examination for change in reflexes and sensation and x rays for *calcification of the vessels of the legs*, pelvis and abdomen are important

Yearly tuberculin tests in the form of the patch technic will prove of value, and the rule for yearly chest x rays for evidence of minimal tuberculosis cannot be overemphasized

HISTORY FORM

NAME AGE M S Tel REF BY NO

FATHER Yrs. F M FAM DR

ADDRESS Mos. W ADDRESS DATE

OCCUPATION RACE BORN Y MO
Parent Husband Patient

FAMILY
F Age M Age Children
S Ages B Ages Spouse
F's F M s F Other Relative
F's M M s M Twins Similar

PAST HISTORY S F Typh Pneu R F Chor Jaun. Tonsil Diph Meas Mumps Pert C P
THERAPY Tet
Pert

Ops Pt Fam

Dev { Teeth, Walk, Speech } Immun { Perg, S F, Diph, S Pox } Allergy { Asthma, Hay fever, Urticaria }
Expos to T B

ONSET Date Sudden Rapid Gradual Indefinite SYMPT

SUGAR FIRST DISCOVERED CAUSE OF EXAM Insurance

LAST PRIOR EXAM Routine

ETIOLOGY Give date of infection or injury if within six months preceding onset
a Obesity b. Heredity 1 Hereditary 2 Familial c Dietary Excess
d Nervous e Infections f Syphilis g Traumatic h Pancreas
i. Endocrine a Thyroid b Hypophysis

DATE

MPT Weight St Av for Hgt Height St Av for Age Date

b Weakness
c Polyuria
d Polydipsia
e Polyphagia
f Pruritus

g Pains
h Extremities
i Cramps
j Mouth
k Bowels

Coma
Reactions
Camp

f Nervous
g Vision

ev St

I

OTHER SYMPT
a Digestive
c Renal

N D V N P b Cir d Resp D C P S Vertigo e C t s Age at onset Pain

PRESENT COMPLAINT

C P units F Now C P units F

Hair Glands C Kuss Dist sounds A I Skin and Mucous Memb E Apparatus

Thyroid
Tonsils
Teeth
Breasts
Rickets

eral appearance
les

Eye Grounds
Breath Acetone
B Pr (recumbent) Syst

Arteries 0 1 2 3 4
Apex size

Spleen Kidneys Knee Jerks Edema Voice

Liver Epid Hernia Pubic Ax Chol

L Induration Ax —— Testes NPN

ay
Dorsalis Pedis R
Insulin Atrophy
Hips
Dev

B s Pubic Fasting Hours P C CO₂ Vols % Sugar %
W B C
R B C
Casts

Diacetic

man Sugar Per Cent S G Alb Acetone

Vol Resc

Neur
Eyes

Neph Pyor B P As Cat T B Ret

FEATURES
Sepsis
Hypo Hept Xanth Epil

CHAPTER XIX

CHILDREN BORN TO DIABETIC MOTHERS—THEIR PRENATAL, PERINATAL AND SUBSEQUENT COURSE

This description of the problems encountered in the prenatal perinatal and subsequent lives of children born to diabetic mothers is based upon an experience with some 1500 cases in which pregnancy complicated diabetes These cases have been observed, treated and studied in the Joslin Clinic between 1898 and 1956 Since 1936 determinations for one or more of the female sex hormones of pregnancy were done on two thirds (1000) of these pregnancies On Feb 26, 1956, 864 of this number had reached the viable period of 28 weeks (the remaining 500 includes patients seen in consultation, those observed prior to our period of study, or those who reported too late for their investigations to be significant) During the past 20 years this "studied" group has been the nucleus of our reports The following descriptive statements refer to cases not receiving female sex hormone treatment, which, as will be seen, appears not only to alter the course and outcome of the pregnancy, but also the histological characteristics of the placenta and of the child

The immediate clinical characteristics of the infant born to the diabetic mother are obesity, edema, congenital anomalies and respiratory distress associated with their neon

mortality According to most authors throughout the world, viable mortality in diabetic pregnancies is 30 per cent and the pre-viable mortality is 20 per cent The subsequent clinical characteristics of the child include gigantism and diabetes

The pathological characteristics are as follows islet hyperplasia, visceromegaly, glycogen nephrosis (excessive extramedullary) hematopoiesis and pulmonary hyaline membranes with atelectasis Because of the increasing importance of this lesion in our cases the characteristics of its pathology are given in detail here In addition to the recognition of the granular eosinophilic hyaline membrane lining the terminal portion of the lungs, the alveolar ducts and the atria, it has now been shown that the membrane lies in the ground substance between a basement membrane lining, the respiratory segment and the basement membrane of the capillary The hyaline membranes sometimes contain fat which does not appear to be significant The main constituent is protein (Millon reaction) The material stains strongly positive with periodic acid Schiff reagent stain (PAS) generally accepted as indicating the presence of polysaccharides, negative by McManus acetylation technique indicating the carbohydrate present in 1 2 glycol linkage and by the McCallum stain there is no fibrin However, Getlin, using immuno chemical technique at the Childrens Hospital, Boston, identified fibrin as the most important constituent of the membranes

Possible Etiological Factors

Not only do a multiplicity of etiological factors operate in the production of the characteristics of this infant but some of them appear to exert their influence over a long interval of time, including not only the pre pregnancy but also the pre diabetic period For many years the influence of the pre diabetic state has been emphasized The prediction of the future development of diabetes through the production of an oversized infant or by fetal pancreatic islet hyperplasia or by the appearance of congenital anomalies has been

utilized by Hoet in his ingenious program for diabetes prevention in the mothers, diabetes and anomaly prevention in their children

Pre-diabetic, Pre-pregnancy, Prenatal and Natal Influences

In our experience there has been slight evidence only of the pre diabetic influence, prior to the tenth year antedating the recognition of diabetes if this is measured by heavy birth weights, but there is no evidence of remote prediabetic influence if measured by the obstetrical course and outcome Statistics for total fetal loss, viable or pre-viable, for incidence of toxemias and for the numbers of infants weighing over 10 pounds were tabulated in 249 recent cases of non-diabetic pregnancies at the Boston Lying in Hospital The total fetal loss was 13 per cent (pre viable 9 per cent, viable 4), toxemia incidence was 3 per cent, birth weights greater than 10 pounds were 3 per cent Among 304 prediabetic mothers whose pregnancies occurred 10 to 40 years before diabetes, the total fetal loss was 14 per cent (5 per cent viable, 9 per cent pre-viable), toxemia occurred in 3 per cent but birth weights exceeding 10 pounds were recorded in 15 per cent As diabetes onset approaches, its effect appears more marked. In forty-four pregnancies within 10 years of diabetes onset, the birth weights exceeded 10 pounds in but 5 per cent, toxemia trebled to 10 per cent and the pre-viable loss was 12 per cent Intrauterine deaths rose from 3 to 9 per cent, neonatal deaths to 11 per cent bringing the fetal loss to 32 per cent In 16 cases where recognition of diabetes occurred in pregnancy the experience was similar—no infant's weight exceeded 10 pounds, intra uterine deaths were 20 per cent, neonatal 5 per cent and the total loss was 30 per cent In the 10-year period after recognition of diabetes the unfavorable influence of diabetes was more marked The fetal loss rose to 44 per

cent, and in the 20 year period after diagnosis fetal loss rose to 80 per cent, the pre viable loss being 73 per cent

Maternal, placental and fetal influences all affect the characteristics and survival of the infant

Maternal

Maternal vascular degeneration and the sudden intensification of the diabetic state affect the course and fetal survival of diabetic pregnancies unfavorably The pre-pregnancy vascular damage of the diabetic woman lessens the chances for fetal survival in proportion to the degree of the vascular lesion Thus, 278 cases were evaluated for their vascular lesions The total fetal loss was 97 per cent among the cases having nephropathies, 87 per cent among those having calcified pelvic arteries and 68 per cent for those having retinopathies, but only 40 per cent in cases showing no evidence of vascular damage The acute vascular response of pregnancy, toxemia, was also associated with increased fetal loss Intra uterine deaths were the most typical failures of these patients with chronic or acute demonstrable vascular lesions Although they occur at any time, the frequency of these deaths has peaked in week 36

The diabetogenic action of pregnancy was most evident in the pre insulin era when the rapid development and progression of ketoacidosis led to fatal maternal termination By the second or third trimester insulin requirements double treble or even quadruple The women *whose insulin requirement is small are affected most* Unaccustomed to the fluctuations of their newly unstable form of diabetes they become easy victims of severe ketoacidosis and hypoglycemia In our series no fetal deaths have been attributed to hypoglycemia but ketoacidosis occurring in the second trimester is highly lethal in its effect upon the infant

Placental Factors

Secretory, vascular, and endocrine failures of the placenta complicate diabetic pregnancies and their harmful influences lower further the chances for fetal survival The strikingly gross characteristic of the placenta is its large size Pathologists state that from its vascular patterns the source of the diabetic placenta is identifiable in part having its origin in patients with vascular degeneration as follows hypertension nephritis or diabetes This observation is confirmed by the evidence found in injected specimens of placentas of diabetic women * They have shown filling failure out of proportion to that found in non diabetics

In diabetes the regulation of the quantity of amniotic fluid is grossly abnormal Instead of the normal amount, 500 to 750 cc the volume increases to some 6000 cc

The endocrine function of the placenta in respect to the production or metabolism of female sex hormone was abnormal in 90 per cent of our cases which showed levels for chorionic gonadotropin from three to ten times the normal between the 24th and 36th week Levels for serum estrogen were lower than the normal and urinary pregnanediol excretions fell to abnormally low levels 17 ketosteroid and 17 hydroxysteroid excretion did not deviate from the values of normal non-diabetic pregnant women Toxemias premature deliveries and intrauterine deaths occurred in association with this imbalance of female sexogens The effect of the placental production of diabetogenic principles upon maternal diabetes has been described

Fetal Influences

The inherited constitution the formation of anomalies in the developing embryo the gross edema and obesity the respiratory difficulties and the disturbed chemistry in the neonatal period all appear to affect the immediate and re-

* Romeny Boston Lying In Hospital.

mote prognosis of the child The genetic constitution for diabetes (homozygote) and for carrier states (heterozygote) is determined at conception Although the frequency of congenital anomalies is great, some 80 per cent, the severity was of major proportion in relatively few In ten per cent of the children the anomalies were lethal or grossly disfiguring Anomalies account for nearly 3 per cent of the perinatal fatalities The incidence in our autopsied cases was 18 per cent, 6 per cent accounting for death Often multiple defects occur and their variety is great They include syndactylia, clawhand, clubfoot, congenital dislocation of the hip, hydrocephalous, meningocele, gross defects of the skull, persistent patent ductus arteriosus, tetralogy of Fallot, coarctation of the aorta, transposition of arterial trunks, blindness, deaf-mutism, agenesis of the esophagus, pyloric stenosis, congenital liver disease, agenesis of kidney, polycystic kidney, agenesis of the bladder and generative organs and monstrosities such as the mermaid type or anencephaly

The obesity and edema of the infant may cause their death when they are delivered through an edematous pelvis These intrapartum deaths occur because, although the head is delivered without too much difficulty, the shoulders jam In the process of difficult extraction the infant dies The first careful description of diabetic pregnancies was that of Benewitz in 1824 His interesting commentary on the presently recognized danger of attempting delivery by the pelvic route of the large infants of diabetic women is as follows

The case is that of a woman, presumably healthy, who had been successfully delivered of four sons The first born died at fourteen weeks of "difficult dentition" The third pregnancy was characterized by vaginal bleeding "on every day of her entire *pregnancy, copiously and continually*"

At the beginning of her fourth pregnancy signs of diabetes developed "A great necessity of drinking and other symp-

toms" which did not, however, prevent a successful outcome, after which "she saw herself again completely freed from all the phenomena of disease " With her fifth pregnancy, symptoms of diabetes again appeared in intensified form Chemical examination of the urine demonstrated "that each pound yielded no less than 2 ounces of saccharine substance, not unlike grain sugar" Description of the "great circumference of her abdomen" suggests hydramnios No fetal motion was noted for one month before delivery

Labor began spontaneously after a pelvic examination, but "after the head was born the shoulders stuck like a wedge in the vaginal outlet and would not go up or down" The infant "seemed anxious and sighed with a clear voice" but was finally stillborn "not without great difficulty" This infant "whom you would surely say Hercules had begotten" weighed 12 pounds and "the arms were of such breadth that I could not encircle their circumference with all my fingers spread"

The prevention and correction of the neonatal respiratory embarrassment continue to defy our therapeutic programs The infant of the diabetic mother may show no abnormal signs and may have a completely normal course or may exhibit respiratory distress immediately after birth Frequently the signs of respiratory distress may be present but minimal at birth and become striking in their manifestations within a few hours following delivery The signs consist of increased respiratory rate, with or without cyanosis, together with retractions of the soft tissues of the chest wall and a constant complaining cry Examination reveals poor aeration of the lungs and inspiratory rales which are inconstant but heard throughout the lung fields X ray reveals a fine granular type of infiltration The respiratory distress becomes increasingly severe over the next hours of life and the infant dies of respiratory failure after 25 to 72 hours, or very gradually begins to improve and recovers completely over the same period Cases coming to autopsy show pulmonary

hyaline membranes In our fatal cases they were present unless congenial anomalies or birth trauma accounted for death

During these early post natal days, certain chemical changes occur Hypoglycemia, to which neonatal deaths were formerly attributed, is now known to be physiological for the first week of life Elevations of the hemoglobin and nucleated red cell counts are comparable in degree to these same findings in normal premature infants Blood oxygen levels may be low Disturbed acid base balance with low *p*H has been reported and such investigations are in prog ress Low levels of potassium and increased excretion of sodium and chloride have been observed in our patients, and elsewhere

In a small series of cases increased levels of desoxycorticosone and increased excretion of 17-ketosteroid and of 17-hydroxysteroids have been demonstrated Eosinophile counts were found to be comparable to those of other newborn infants

Infancy and Early Childhood

Congenital anomalies exact their toll in the infancy period between two weeks and twelve months For the most part they are cardiac in nature From the end of the first year up to age six, the behavior of these children is not remarkable

At age six the excessive rates of linear growth and exces sive gains in weight become manifest A series of 105 chil dren* of our diabetic mothers showed at the time of their examination when they were from 18 months to 20 years of age that gigantism was prevalent among sons, 57 per cent of whom were from 3 to 10 inches above the Englebach standard, and 50 per cent of them weighed more than 30 pounds above the standard weight for height and age Daughters showed the same plus deviations in 31 per cent

* White, P, Duckers J, Koshy, P, *The Med Clin. of N.A.*, Vol 37, No 5, 1953

for height and 20 per cent for weight Twenty-one per cent of the boys rated greater than the 2% auxodrome level on the Wetzel grid and fell in channels A_3 and A_4 as did 14 per cent of the girls Bone development estimated by comparison with the Todd atlas exceeded the chronological age by 12 months in 48 per cent of the cases Congenital anomalies were found on physical examination in 17 per cent

A second striking deviation from the normal was the evidence of diabetes In the general population one child in 2500 develops diabetes In this population 9 per cent showed undoubted diabetes and 14 per cent showed borderline glucose tolerance curves with capillary blood sugar values between 200 mg and 250 mg Another deviation from the normal was an apparently well defined change of the vascular pattern of the smaller vessels in the conjunctiva examined at the microscopic level This occurred in 75 per cent of the children classified as diabetic or borderline A positive correlation was found between the degree of vascular change in the smaller blood vessels of the conjunctiva the abnormal glucose tolerance tests and the high Wetzel grid rating *

For Comparison and Evaluation

Comparable data were collected on children of diabetic fathers The survival rate of their offspring is high, viable survival being that of the general population Heavy birth weights of infants of pre-diabetic and diabetic fathers have been described † Seven per cent of the infants of pre-diabetic fathers and 1 per cent of the infants of diabetic fathers in this series were more than ten pounds at birth

Using identical standards, the positive deviations for weight of more than 30 pounds were found in only 4 per cent of the sons and 2 per cent of the daughters of diabetic

* Ditzel, J., White P., Duckers J., *Diabetes* 3 99-106, 1954
† Jackson, P., *Lancet* 2 625-231, 1955

hyaline membranes In our fatal cases they were present unless congenial anomalies or birth trauma accounted for death

During these early post-natal days, certain chemical changes occur Hypoglycemia, to which neonatal deaths were formerly attributed, is now known to be physiological for the first week of life Elevations of the hemoglobin and nucleated red cell counts are comparable in degree to these same findings in normal premature infants Blood oxygen levels may be low Disturbed acid base balance with low *p*H has been reported and such investigations are in progress Low levels of potassium and increased excretion of sodium and chloride have been observed in our patients, and elsewhere

In a small series of cases increased levels of desoxycortisone and increased excretion of 17-ketosteroid and of 17-hydroxysteroids have been demonstrated Eosinophile counts were found to be comparable to those of other newborn infants

Infancy and Early Childhood

Congenital anomalies exact their toll in the infancy period between two weeks and twelve months For the most part they are cardiac in nature From the end of the first year up to age six, the behavior of these children is not remarkable

At age six the excessive rates of linear growth and excessive gains in weight become manifest A series of 105 children* of our diabetic mothers showed at the time of their examination when they were from 13 months to 20 years of age that gigantism was prevalent among sons, 57 per cent of whom were from 3 to 10 inches above the Englebach standard, and 50 per cent of them weighed more than 30 pounds above the standard weight for height and age Daughters showed the same plus deviations in 31 per cent

* White P, Duckers J, Koshy, P, *The Med Clin. of N.A.* Vol. 37, No 5, 1953

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entire period of pregnancy and 96 per cent for the viable period after week 28

An ingenious program for prevention of the pre-diabetic influence has been conceived, developed and applied by Professor Hoet *

Program to Prevent Effect Produced by Vascular Degeneration

The program for prevention of the harmful influence of pre pregnancy vascular disease consists of three parts (1) identification of patients with vascular damage and grading them according to their influence upon fetal wastage, (2) attempts to increase vascularity, (3) elective delivery before the *failure* of pelvic vascular reserve Patients with no vascular damage are separated from those where it is not revealed, but possible because of the duration of diabetes and its age of onset, and from the groups where progressively severe vascular disease develops in the form of retinopathies, calcified pelvic arteries and nephropathies

Increased vascularity is one of the functions of estrogenic hormones and is one of the reasons for their use which will be described in detail under "placental influence"

The characteristic time at which intra uterine deaths occur, namely in week 36, gives presumptive clinical evidence of premature placental vascular insufficiency Evaluation of patients with demonstrable vascular degeneration at the end of week 35 is essential Postponement of delivery beyond this week must be considered cautiously Mild toxemia in diabetics must be given this same cautious evaluation.

Control of Diabetes

Because of the well-known diabetogenic action of pregnancy and the susceptibility of these patients to ketoacidosis and hypoglycemia, chemical control of diabetes is stressed The methods employed are described on page 278

* Hoet, *Diabetes*, 3, 1, 1954

fathers The comparable positive deviations in height were 31 per cent for both boys and girls The bone growth was advanced in 35 per cent of the children of diabetic fathers Congenital anomalies were found on physical examination in 15 per cent. Twenty one per cent of the children of dia betic fathers had abnormal glucose tolerance curves Of these 9 per cent had undoubted diabetes and 12 per cent had borderline curves with capillary bloods ranging from 200 to 250 mg

Similarities and differences therefore existed in the com parable offspring of diabetic mothers and fathers The most striking of these differences was the positive deviation of weight in the children of diabetic mothers whose sons ex ceeded the expected weight by 30 pounds in 50 per cent, whereas the sons of diabetic fathers exceeded the expected weight in this amount in only 4 per cent Among the daugh ters of diabetic mothers 20 per cent whereas among the daughters of diabetic fathers 2 per cent showed this positive deviation Sons of diabetic mothers showed greater positive deviations in height—more than 3 inches greater than the expected in 51 per cent sons of diabetic fathers in 31 per cent Birth weights were more often higher and bone age more often advanced in children of diabetic mothers

In the two characteristics which concern us the most anomalies and diabetes the incidence was nearly equal The search for anomalies should be extended to include roentgen x ray studies Lethal anomalies were excluded by the nature of this comparative study

Objectives Management

From the foregoing it is evident that the objective in our management of pregnant diabetic women and their children is the removal of the harmful maternal placental and fetal influences so that the total fetal and infant survival in dia betes will approach the normal namely 87 per cent for the

ence the frequency of pulmonary hyaline membranes The preventive management includes trials of labor for pelvic delivery and Cesarean section reserved for failures New methods of medical induction make it possible to deliver more of these cases through the pelvis at our early elective date The neonatal management of the infant includes aspirat on of the stomach and of the upper air passages dehydration by postponement of feedings for some 48 hours oxygen of low concentration antibiotics and chemotherapy

Results

The viable fetal salvage in 719 cases receiving female sex hormone therapy is 88 per cent In our 400 most recent cases delivered at the Boston Lying In Hospital since August 1950 pre-viable losses were only 9 per cent The viable survival in cases receiving female sex hormones without vascular disease is 91 per cent (total 84 per cent) with retinopathies viable 85 per cent (total 70 per cent)

Among patients receiving female sex hormones the structure of the placenta is described as normal and with two exceptions the characteristics described as those of the infants of diabetic mothers have disappeared The exceptions are as follows islet hyperplasia and pulmonary hyaline membranes The degree but not the incidence of hydramnios has been reduced Intrauterine deaths have fallen from 15 per cent to 3 per cent pre viable losses from 20 to 9 per cent and neonatal, 15 per cent to 7 per cent Losses due to congenital anomalies have remained unchanged

Birth weights due largely to fat and edema have been reduced in degree but still exceed the normal for period of gestation The weights average one pound less than for cases not receiving female sex hormonal therapy

Discussion

The influence of the pre-diabetic state upon the child of the diabetic mother in respect to birth weight increases as diabetes

Although poor chemical control complicated with acidosis favors fetal loss good chemical control possible to maintain by weekly visits to the physician and pre-delivery periods of hospitalization has not guaranteed fetal survival The average third trimester blood sugar for our mothers whose infants did and did not survive were identical and of normal value

Management of abnormalities arising from disturbed placental function have been described in chapter on Pregnancy and are summarized here Placental function is disturbed in at least two ways regulation of
fluid and
ture de
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Management for Influences in the Embryo Fetus and Infant

The highest correlation in pre viable fetal losses is with frequency and degree of vascular damage After 20 years duration of diabetes or with calcified pelvic arteries or nephropathy pre-viable losses approached 75 per cent. Estrogenic protection for these groups as a whole appears essential

In programs for prevention of congenital anomalies careful chemical control to avoid the hypoxia associated with ketoacidosis hyperglycemia or hypoglycemia cannot be overemphasized in these early weeks, as well as the preventive care with infections

Prematurity Cesarean section and diabetes per se as well as hyperoxia fall of blood pressure and anesthesia all influ

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onset approaches The total pre-diabetic influence is one of lesser degree than the harmful influence of recognized diabetes Mechanisms operating through the pituitary, adrenal and pancreas are probable

Fluid and endocrine imbalance, disturbance of vasomotor responses and degenerative vascular disease have a profound effect upon the survival and subsequent course of children born to diabetic mothers In sequence of time the first harmful effect is the change in the diabetic state Hypoglycemia complicates the early weeks when presumably chorionic gonadotropin inhibits anterior pituitary activity and this blood sugar lowering action is further intensified both by inadequate food intake and by inadequate absorption of the food taken Hypoglycemia, through its pituitary adrenal cortex action, produces vasoconstriction and thereby hypoxia Hypoxia, early in pregnancy, could thus contribute to the production of congenital anomalies The mechanism of harmful influence in pre existing vascular disease can be explained in similar fashion It interferes with an adequate blood supply for the uterus and thereby for the placenta

The increased placental production of adrenal steroid hormones, ACTH and cortisone, as well as of growth hormone, commencing in the fourteenth week of pregnancy, appears to explain the increased insulin requirement It is progressive in nature so that by the third trimester of pregnancy the dose of insulin may have trebled or quadrupled

The disturbed regulation of amniotic fluid may represent failure of absorption The diminution of blood, oxygen and glucose to the placenta due to maternal vascular disease and altered maternal vasomotor responses may be inferred Eventually placental development and function fail Aging of the placental vessels to the point of obstruction ensues These inferred altered vasomotor responses are possible because the known affectors of vascular responses are present (constriction from low CO_2 tension, cortisone, ACTH and stress) These altered responses may then produce exudation with failure of reabsorption of fluid Factors, probably endocrine, favor retention of sodium and must be evaluated further.

The placental failure of production of female sex hormones may be explained on the basis of rapid maturity and aging due

to maternal anterior pituitary influences, hyperglycemia or advanced maternal vascular degeneration Early peaking of hormones and early failure of production, pathological now instead of physiological may occur Female sex hormones increase vascularity and stimulate the placental pituitary relation and replace the hormonal defect

Control of infants' weights has followed the use of female sex hormonal therapy Without therapy infants weights for the same gestational age were one pound more than in cases receiving estrogen and progesterone The inhibition of the pituitary by estrogen may be the effective mechanism Hyperglycemia and *chorionic gonadotropin or hyperpituitarism hyperadrenocorti* coidism of maternal placental or fetal origin may produce the "Cushingoid" type of infant

Pulmonary hyaline membranes were present in all autopsied cases where there was no other adequate cause for death * The site of the hyaline membranes in the ground substance between the basement membrane of the lung segment and the capillaries suggests an endogenous mechanism A possible mechanism is as follows Fluid exudes from the capillaries responding to the fluctuating metabolic state of diabetes With respiration at birth there is inspiration of amniotic fluid The fibrinogen from the pulmonary capillaries contacting the thromboplastin derived from amniotic fluid produces the fibrin which has apparently been identified as an important constituent of the hyaline membranes Hyperoxia, hypoxia, anesthesia, and fall of blood pressure may be factors in vasomotor responses leading to the formation of the exudate The frequency of hyaline membrane increases with prematurity and Cesarean section Prenatal management, chemical control of diabetes supplemented with female sex hormones will favor prolongation of pregnancy

The gigantism observed in the children of diabetic mothers did not occur in the children of diabetic fathers The islet hyperplasia found at birth suggests possible overproduction of insulin, the hyperplasia being attributed to maternal hyperglycemia In Mayer's obese mice the insulin content of the pancreas is greater than that of normal mice The incidence of diabetes children of diabetic fathers was almost identical with the

* Winter, W D, Gellis S *Amer J Dis Child*, Vol. 87, p 9,

dence of diabetes in children born to diabetic mothers In si teen children where both parents had diabetes, the incidence clinical and chemical diabetes was 62 per cent, favoring the co cept that the transmission of diabetes passes through Mendel recessive genes Steinberg* calculates that one out of every thr individuals carries a gene for diabetes On this basis the e pected incidence of diabetes when one parent has the disease 22 per cent Our findings in children born to diabetic mothe and for children of diabetic fathers approximates this closely, per cent for the former and 21 per cent for the latter At pre ent these results do not favor the concept that maternal i fluences favor the subsequent development of diabetes in th child † More careful control studies in relation to congenit anomalies both with respect to frequency and type in the of spring of diabetic women and in the offspring of diabetic me are essential

In our experience pre diabetes, although influencing th immediate and remote course of infants born to these moth ers, was less injurious than diabetes per se which if of shor duration in turn was less serious than diabetes complicate with vascular degeneration

Chemical control of diabetes diminishes the hazards o fetal death from hypoglycemia and ketoacidosis to whic the intensification of diabetes from the placental productio of diabetogenic hormones makes diabetic women liable

Estrogen and progesterone appear to increase vasculari and decrease the fetal mortality related to vascular damage Female sex hormonal therapy appears to prevent the vascu lar change characteristic of the diabetic placenta, stimulate the placental pituitary relations and replaces the hormona deficit, lessening the chances for fetal loss due to the rapid maturity of the placenta

Of the six possible explanations for the poor behavior and neonatal deaths in infants born to diabetic mothers hypo-

* Steinberg A G *Eugenics*, Vol. 2 No 1, March 1955

† We have seen but one congenital diabetic age 9 days surviving to 42 days The pancreas showed extensive islet pathology

glycemia, congestive heart failure, primary pneumonia, respiratory acidosis, hypokalemia and pulmonary hyaline membranes with atelectasis, pulmonary hyaline membranes appears to be the most significant (Hypoglycemia is physiological, the pneumonia is secondary, congestive heart failure is not proved and respiratory acidosis may be effect rather than cause) Programs for prevention and treatment of pulmonary hyaline membranes based upon the concept that they are of both endogenous and exogenous origin are in progress

Gigantism in the child between ages 6 and 16 appears to be influenced by the maternal diabetic state It did not occur commonly in children of diabetic fathers Overproduction of insulin by their hyperplastic islets may promote the excessive rate and quality of growth

The susceptibility of the child both of a diabetic mother and of a diabetic father to diabetes is established and is apparently revealed by glucose tolerance tests even before age twenty The data support the concept that the transmission proceeds through Mendelian recessive genes Programs for identification of diabetes and protection during diabetogenic experiences must be organized

Female sex hormonal therapy increasing vascularity when added to chemical control of diabetes, measures to prevent or correct hydramnios, careful selection of time and type of delivery have raised fetal and infant survival to nearly 90 per cent which, in turn, approaches the normal of 96 per cent

CHAPTER XX

THE EXAMINATION OF THE URINE AND BLOOD

The Necessity of Urine and Blood Tests

The discovery of sugar in the urine is frequently the first suggestion of the diagnosis of diabetes Because of the importance of the early detection of diabetes before any symptoms have been noted by the patient, routine and repeated testing of the urine, not only of all patients but also of the supposedly healthy, is a necessary part of the physician's function today The Diabetes Detection Drive, sponsored annually since 1948 by the American Diabetes Association, has left no doubt of the value of routine testing of the urine among persons in the general population and especially when such tests are followed by examinations of the blood to confirm the diagnosis by instruction and continued prophylactic care of the patient In all illnesses, especially of an infectious nature, examinations of the urine should be made for sugar and for albumin especially at the termination of treatment or before the discharge of the patient Already the importance of securing both urine and blood specimens an hour after a meal rather than in the fasting condition has been emphasized It is only by this procedure that one may avoid missing the diagnosis when urine and blood is obtained only before breakfast in the morning In doubtful cases it should be remembered that sugar may appear only after certain meals and, therefore, repeated examinations

of the urine should be made not only after the first but after later meals

Without examinations of the blood sugar, both the diagnosis and the treatment of the patient found to have sugar in the urine rest on an insecure foundation

A Examination of the Urine

The volume of urine passed in 24 hours varies in the average normal person from 1000 to 2000 cc, according to fluid intake and varying losses of water through the skin and the lungs In diabetic patients the amount frequently parallels the amount of sugar in the urine but the relationship between volume, specific gravity and sugar percentage is so varied that neither specific gravity nor volume may be relied upon as a diagnostic measure

If the volume of urine is expressed in cubic centimeters, then the amount of sugar in the 24-hour quantity is easily calculated A fluid ounce is actually 29 6 cc but in clinical work it is reasonable to reckon it as 30 cc One quart is the equivalent of 946 cc but sufficient accuracy is obtained if one considers it to be 1000 cc Patients should be instructed in methods of quantitating sugar in the urine and then by collecting their 24-hour amount perhaps once or twice a week be enabled to have a quantitative record of the amount of sugar which is being excreted Such measures, although not necessary in all patients, nevertheless may be of great value in the treatment of more severe and unstable patients

The specific gravity of the urine normally is on the average about 1 015 to 1 025 In uncontrolled diabetes this value may be very high. However, normal specific gravity does not eliminate the presence of glycosuria

Non-diabetic Glycosuria

If two to five per cent of the population tested show glycosuria, from one fifth to one-tenth of them will prove

to have diabetes Therefore, the differential diagnosis is essential.

Glycuresis is the name applied to the phenomenon observed in normal persons in which a positive copper reduction test is obtained essentially without an increase of the blood sugar It is due to excretion of small amounts of glucose and unassimilable carbohydrate

Alimentary glycosuria is noted following the ingestion of large quantities of sucrose, glucose or starch in normal individuals without an increase in blood sugar

Renal glycosuria is the name given to the condition in which glucose appears in the urine at all times and yet the blood sugar level is normal both fasting and after meals

The actual glucose content of normal human urine is ordinarily as low as 0 002 to 0 01 per cent It is not increased by variations of food intake and it is ordinarily not shown *by clinical tests*

Glucose in Urine

Without quantitative knowledge of the total quantity of sugar excreted in 24 hours it is difficult to evaluate properly the degree of control of diabetes The sugar in the urine of the diabetic usually varies directly with the quantity of carbohydrate forming material in the diet, to a less extent with the protein and still less with the fat, except as these influence the total caloric intake

(1) *Qualitative Tests* Most of the qualitative tests for glucose have the advantage that although traces of sugar may be present in the urine of normal individuals they do not give a positive test unless the sugar exists in an amount greater than normal The Benedict test has been the test most generally used, because it requires only a single solution which keeps indefinitely and it offers less frequent error than some other tests The test is carried out as follows

Four drops of urine are placed in a test tube and to this

are added 2 5 cc (one half teaspoon) of Benedict s solution If eight drops of urine are used, then 5 cc of Benedict s *solution must be employed The tube is shaken to mix the* urine and the solution and then placed in water that is already boiling If a number of tests are to be made at once, time may be saved by using a large water bath and a wire test tube rack After being in the boiling water for five minutes, the tube or rack is removed and examined for evidence of reduction In the presence of glucose the entire body of the solution when shaken will be filled with a precipitate which is greenish, yellow or red in color, according to whether the amount of sugar is slight or considerable Particularly, if 4 drops are used with 2 5 cc of Benedict s *solution, the test should be carried out in boiling water* rather than over a free flame because of evaporation of the solution If 5 cc of Benedict s solution and 8 drops of urine are employed, as in the original test, the solution may be boiled over a free flame for two minutes in which case a pyrex test tube should be used

The test is delicate enough to detect a quantity as small as 0 08 to 0 1 per cent sugar with a faint pea green change in color This green color gives place to yellowish green when the urine contains 0 5 per cent sugar In percentages over 1 0 per cent the color becomes yellow or orange or brown Occasionally urine specimens so tested give a fluorescent appearance due to a fine, brick red precipitation of the copper oxide Apparently some severe diabetics show such a reaction after eating certain fruits or when on very low diets On actual quantitation often such urines which seem deceptively moderate in quantity of glucose may be found to have a good deal more sugar

Other sugars such as lactose galactose, pentose and levulose reduce Benedict s solution and if the blood test is normal their presence must be suspected Modifications of the Benedict test have included the "Clinitest" in which a reagent tablet is dropped into a measured amount of diluted

urine Heat is generated with the reaction with the resultant boiling which lasts for a few seconds The colors produced by varying amounts of sugar are roughly those of a standard Benedict test and are interpreted according to a color scheme

Tests which depend upon reduction of bismuth in alkaline solutions have been employed, such as that of Nylander A present day modification is found in the Galatest in which a gray alkaline tablet containing bismuth is used A drop or two of urine is placed on a mound of the powder and the presence of sugar is indicated by the production of a gray or black color

The most recent and simple test appears to be the Tes-Tape, which is based upon a specific biologic test for glucose About an inch of prepared paper tape is moistened with the urine The area will remain yellow if the specimen is free from sugar and change from varying shades of green to a dark blue green, depending upon the quantity of sugar present The reading should be made at the end of two minutes and the darkest part of the tape is recorded. This is an excellent method for patients and the tape may be placed upon a record form and the Tes-Tape test presented to the physician for inspection Clinistick, also new, depends upon a similar reaction

(2) *Quantitative Tests* Methods for quantitating the sugar in the urine with sufficient accuracy for clinical work can easily be performed by the general practitioner, the nurse, the doctor's secretary, or by intelligent patients in the home The Clinistick and Tes-Tape give a reasonable approximation of the percentage of sugar in the urine

The quantitative tests are described in original articles and standard books on laboratory procedures The quantitative Benedict test is described here The original method is too time consuming for routine use, and a micro-modification is most practical The method, devised by Millard

Smith, can be performed in a minimum of time It is simple, and if carried out carefully furnishes reliable data The apparatus needed consists of a small ring stand with test tube clamp a micro-Bunsen burner or small alcohol lamp, a pyrex test-tube (18 by 160 mm), a Millard Smith pipette No 2 and a 1 cc Ostwald pipette With the Ostwald pipette 1 cc of Benedict s original quantitative solution may be transferred into the test-tube and 0 2 to 0 7 gram of anhydrous sodium carbonate should be added A small well dried pebble, a piece of quartz, or a pinch of powdered talc should also be added to prevent bumping The mixture is heated to boiling and the urine added from the Smith pipette drop by drop until the reduction is complete as evidenced by the disappearance of the blue color The percentage of sugar may then be read directly from the pipette Urine specimens containing 1 per cent of sugar or less may be titrated directly, while those containing over 1 per cent should be diluted (1 to 10 or 1 to 20) before titration All dilutions of the urine reduce the accuracy of the results obtained, due to lowered concentration of the urinary salts For rapid reduction of the reagent vigorous boiling is essential, which may result in too rapid evaporation This is avoided by allowing more time for reduction between additions of urine The best results are obtained if the urine is added slowly and if the solution is kept at the boiling point by manipulation of the flame A very small flame should be employed The tendency in titration is to go past the end-point, since the reduction does not take place as rapidly as in many titrations to which one is accustomed When nearing the end point, the urine must be added slowly In urine of low sugar content the boiling should be rather vigorous at first in order to maintain a constant volume, while 1 to 2 cc of urine necessary to give complete reduction are being added With a moderate amount of practice the regulation of the volume of the boiling solution becomes quite

simple. Other quantitative methods may be mentioned. Sheftel devised a simple method dependent upon a comparison of the colors produced by the reduction of a copper reagent with the colors of a color chart. The Di-Nitro-Salicylate method of Sumner and Exton combines speed with accuracy. Polariscopy and fermentation tests may be employed, but these methods are by no means as accurate or satisfactory as chemical methods and are seldom used. Covey has described an adaptation of the fermentation method for use by the blind. The presence of sugar is indicated after incubation by the bulging of a rubber diaphragm covering the mouth of a tiny bottle containing a bit of yeast and filled with urine.

Tests for Other Sugars

Lactose, pentose, fructose, maltose and sucrose are found in urine sufficiently often to make necessary the use of special laboratory tests to determine the type of sugar in all cases of non-diabetic melituria. For accuracy such suspicious urine should be subjected to examination by qualified chemists.

Certain substances occurring in the urine may cause confusion in urine tests. Among these may be mentioned creatinine and uric acid, especially in urine which is highly concentrated. Various drugs, including salicylates, especially when large doses have been given, may give falsely positive tests for sugar, as has been reported also in patients receiving massive doses of penicillin.

The Determination of "Ketone Bodies" in the Urine

The importance of utilizing simple qualitative tests for the detection of acidosis or early coma cannot be overemphasized. *Every doctor should carry* in his bag not only the means of testing the urine for sugar but solutions such as ferric chloride or test powders for acetone so that immediate tests can be made at the bedside as a diagnostic procedure.

Diacetic Acid (Aceto-acetic acid)

The simplest and most useful method for the detection of clinical acidosis due to ketosis by urine examination is Gerhardt's ferric chloride reaction The method of testing follows

To 5 or 10 cc of freshly voided urine carefully add a few drops of 10 per cent aqueous solution of ferric chloride A precipitate of ferric phosphate first forms, but upon the addition of a few more drops is dissolved The depth of the Burgundy red color obtained is an index to the quantity of diacetic acid present The intensity of the reaction may be roughly recorded as 1, 2, 3 or 4 plus

Diacetic acid occurs in the urine in diabetics under the same conditions as acetone and is rarely found except together with acetone Indeed, acetone merely represents diacetic acid, from which in the process of decomposition one molecule of CO_2 has been removed

It must be remembered that if a patient is taking salicylates, antipyrin, cyanates, or acetates, the ferric chloride test will give a similar red color Error can be avoided if the solution is boiled for two minutes Diacetic acid is unstable and it disappears, whereas the red color caused by the above mentioned drugs does not disappear upon boiling We, routinely, do a sodium nitroprusside test on urine specimens with a red color in order not to be deceived by a masking due to the drug reaction

Acetone forms a very small part of the ketone bodies or the acetone bodies in fresh urine The older the urine, the greater the change of diacetic acid into acetone and therefore, the larger amount of acetone The Rothera test is much more sensitive for acetoacetic acid than for acetone For the practising physician the specially prepared nitroprusside reagents in powder or tablet form, which permit t detection of acetone in the urine, are available made by the Ames Company, Elkhart, Indiana, B

Company, Worcester, Massachusetts, and the Denver Chemical Company, New York

Beta oxybutyric acid may not be recognized by any simple qualitative tests

Quantitative tests as a measure of the severity of ketosis are available but are no longer commonly employed in ordinary clinical study More informative data can be obtained by blood study The quantitative determinations of beta oxybutyric acid, the 24 hour ammonia excretion and the total titratable acidity may be found in standard laboratory texts

Other tests Tests for albumin in the urine have become of increasing importance because of the frequency with which nephropathy occurs in patients with diabetes of long standing The test should be performed at frequent intervals in such cases Two tests for albumin in the urine which the authors employ are that with suphosalicylic acid (2 per cent in 0 5 per cent acetic acid) and that with Roberts reagent (1 volume concentrated HNO_3 and 5 volumes of a saturated solution of $MgSO_4$ The amount of albumin may be estimated by a simple, rapid technique described by Kingsburg, Clark, Williams and Post This method consists of adding 4 5 cc of 3 per cent sulphosalicylic acid to 1.5 cc of clear, centrifuged urine in a specially marked tube, mixing letting stand for ten minutes, and comparing the turbidity produced with that in standard tubes It is much more satisfactory to express the amount of albumin in terms of milligrams per 100 cc of urine rather than in the indefinite terms of slightest possible trace, very slight trace, etc

Tests of renal function, including the phenolsuphonephthalein test, the concentration test and the blood non protein nitrogen, are in common use

B The Examination of the Blood

In few, if any, other chronic diseases commonly treated by family practitioners are chemical examinations of the blood at intervals and in emergencies so important for success in treatment Blood sugar determination may be essential not merely for diagnosis but for the proper adjustment of treatment from time to time Because of the many complications occurring with increasing frequency because of the striking prolongation of life of diabetic patients, a variety of other chemical tests may be essential

Collection of the Blood

Blood sugar determinations may be made either in capillary blood or in venous blood obtained by venepuncture We find increasing advantage in the use of the micro methods, particularly avoiding venepuncture in children and also during emergencies as a means of protecting the veins of patients who may be receiving intravenous therapy over a period of time However, we still employ venous blood on many occasions Blood obtained from the antecubital veins or in emergencies from other veins have advantages over capillary samplings

(1) The only requirement in obtaining venous blood is that a sufficient quantity of blood be put in a container where it is mixed with an anticoagulant and with a substance which will prevent decomposition of the glucose With capillary blood, some skill and care are necessary to measure with a pipette exactly 0 1 cc of blood with sufficient speed to avoid clotting
(2) With the larger quantity of blood from a vein, determinations of more than one chemical in the blood may be obtained from the single sample

Blood is usually drawn from a vein in the •
space with the use of a 5 or 10 cc syringe and a 21

needle Both syringe and needle should have been sterilized by autoclaving or adequate boiling to prevent the possibility of transmitting infectious agents, particularly of viral hepatitis Two to 10 or more cc of blood are withdrawn, depending upon the determinations which are desired The blood is placed in 1 ounce, wide mouthed bottles in the bottom of which has been placed a small amount of a mixture of 5 parts sodium fluoride to 2 parts powdered potassium oxalate *in the amount of 7 milligrams of the mixture* per cc of blood Blood which has been mixed with sodium fluoride will retain its sugar content at room temperature for at least several hours and even for days if kept in the refrigerator When blood is withdrawn for determination of carbon dioxide content of plasma (blood taken under oil) or for a determination of blood cholesterol, a satisfactory anti coagulant is potassium oxalate

For most determinations of blood constituents in which colorimetric comparisons are used, the photoelectric colorimeter is recommended

Blood Sugar

Determinations of the blood sugar have become *essential* in differentiating cases of non diabetic glycosuria Such patients really form 15 per cent of the patients consulting the Joslin Clinic The matter is becoming more difficult as the number of individuals with known diabetic heredity increases and the transition from the pre clinical to the clinical diabetic state presents diagnostic problems

In addition to the importance of diagnosis the practitioner will find as he follows diabetic patients over the years that changes in the level of the fasting blood sugar may serve as a helpful guide in measuring the increasing or decreasing severity of diabetes More important *still, the level of the* blood sugar in the fasting condition will be of great value, *together with urine tests, in deciding* whether or not the action of such long acting insulins as protamine zinc in

sulin, NPH, Lente or Globin insulin, is adequate The action of these insulins is longer if the dose is larger, but their action is also influenced by exercise and the diet *Blood sugar measurements*, particularly at 3 30 or 4 00 in the afternoon aid in determining whether or not such insulins as Lente and Globin are reducing the blood sugar to levels which may lead to a hypoglycemic reaction

The ideal blood sugar method should eliminate the effect of non glucose substances consisting of glutathione, ergothionene and creatinine, which are included in the Folin Wu and similar blood sugar methods These substances do vary in amount, although they, usually, are credited with providing only 15-30 mg per 100 cc of the total blood sugar We have continued to use the Folin Wu method as follows

Transfer 2 cc of the tungstic acid blood filtrate (or 1 cc plus 1 cc. of water if very high blood sugar values are expected) to a Folin-Wu sugar tube graduated at 25 cc and to other similar tubes add 2 cc of standard sugar solutions containing 0 2 and 0 4 mg respectively of glucose To each tube add 2 cc of the alkaline copper solution The surface of the mixtures must now have reached the constricted part of the tube Transfer the tubes to a rapidly boiling water bath and heat for 8 minutes Cool in running water Add to each test tube 2 cc of phosphomolybdic acid reagent. After about one minute dilute to the mark with water and mix It is essential that adequate attention be given to this mixing because the greater part of the blue color is formed in the bulb of the tube. Read in calibrated photocolorimeter

For obtaining "true glucose" the *Somogyi Nelson method* is employed

Particularly *for children and in cases of coma or shock* the micro blood sugar method is most valuable od which we have employed is that of Folin and *laked blood*

Cholesterol and Lipids

The importance of serum cholesterol and lipids in diabetic patients has long been known as an evidence of severe and uncontrolled diabetes However, at present the wide spread interest in the lipid metabolism and particularly cholesterol values in relation to premature arteriosclerosis have given these determinations added value They are, therefore, carried out particularly in young patients of long duration, in whom the onset of degenerative complications is feared The methods of Bloor and his associates may be found in standard textbooks

Carbon Dioxide in Blood Plasma

In diabetic patients not under good control with insulin and a balanced diet, a loss of base may occur over long periods of time even without severe ketosis However, when acidosis and ketosis develop, then there may be an excessive loss of base and fall in the alkaline reserve capacity of the blood for CO_2 Normal values vary between 25 and 34 milliequivalents per liter (55 to 75 volumes per cent) When such values have fallen to 12 or 15 mEq serious acidosis is present We routinely, use the standard method of Van Slyke for determination of the carbon dioxide content of the plasma collecting blood samples under oil

Acetone in the Blood (See page 117 in section on Diabetic Coma)

CHAPTER XXI

DETERMINATIONS OF PREGNANEDIOL, 17 KETO AND 17 HYDROXYSTEROIDS, AND ASSAYS FOR CHORIONIC GONADOTROPHIN

Urinary Pregnanediol

Because the authors believe that an imbalance of female sex hormones characterizes abnormal pregnancy in diabetes and that female sex hormonal therapy is indicated, quantitative determinations for urinary pregnanediol are done upon the pregnant diabetic women under their care

The technique described in the *Journal of Biological Chemistry* in 1941 by Astwood and Jones has been employed in our patients The technique is as follows The method involves primarily four steps

1 Liberation of free pregnanediol from Na pregnanediol glucuronidate by acid hydrolysis of the urine in the presence of toluol
2 Separation of most of the phenolic contaminants from the filtered toluol extract by the addition of 2% Na OH in absolute methanol
3 Further removal of most of the impurities by precipitation with alcoholic alkali
4 Final quantitative crystallization of pure pregnanediol from aqueous alcohol

Method

The entire 24 hour urine specimen is collected, preferably with a few drops of toluol as a preservative The entire 24-hour amount is used if it is less than a liter, or a suitable aliquot (generally 1 liter) is taken In late pregnancy 50-500 ml may be used, depending on the amount of NaPG excreted

Procedure for 1 liter Place 1 liter of urine in a 2 liter round bottom flask Add 50 ml toluol per liter, a few anti-bump stones, and connect the flask to a wide bore reflux condenser Heat to boiling over an electric plate Add 100 ml *of concentrated C P HCl per liter slowly through the* condenser and continue to boil for 15 minutes (temp is 105°-110°) Cautiously remove flask to a vessel of cold water Do not shake Bring to room temperature Transfer to a 2 liter separatory funnel Remove toluol layer and toluol urine emulsion layer and save Re extract urine layer twice with 25 ml portions of toluol Filter combined toluol extracts and urine emulsion through Buchner funnel If done slowly, the emulsion is thoroughly broken down Wash residue completely with 3 small lots of toluol Transfer filtrate to a 250 ml separatory funnel, discard urine layer, and wash once with *50 ml* water

Transfer toluol extract to a dry 250 ml round bottom side-arm distilling flask, add a few anti bump stones, attach to a condenser and distil until all the water is removed, using an electric plate (Temp 110°) Remove flask from electric plate and add carefully to the reaction flask by means of a pipette or preferably a 50 ml dropping funnel 10 ml of 2% NaOH in abs methanol Return to electric plate and continue boiling until the alcohol is completely driven off (temp again 110°) and approximately 10 ml toluol remains If the precipitation that settles out is very gelatinous add 0 5 to 1 0 gm anhydrous CaO *to the hot flask on removing* from the condenser

Let stand at room temperature until cool and filter through a sintered glass funnel with gentle suction into a 125 ml. Erlenmeyer filter flask. Wash precipitate thoroughly with 8-10 ml portions of toluol The filtrate should be clear of all traces of pink or brown color If it is not, repeat the NaOH addition Transfer the clear pale greenish yellow filtrate to a 250 ml side arm distilling flask, add an anti bump stone, and distill to near dryness When cool, transfer the residue from distilling flask to a 125 ml Erlenmeyer using absolute ethanol

Remove the last few ml of toluol and alcohol by a vacuum while heating the flask on an oil bath or other suitable anhydrous medium taking care not to overheat the residue *Add 10 ml of absolute ethanol and completely dissolve the* residue by heating if necessary While heating add dropwise from a burette 40 ml of aqueous 0 1 N NaOH Stopper, let stand at room temperature until cool, and place in refrigerator overnight

Collect precipitate by using sintered glass funnel and continuous refiltering if necessary to obtain an almost clear filtrate Wash with water, then with a few ml of Benzine (petroleum ether), dissolve in 10 ml of absolute ethanol and precipitate a second time, using 30 ml distilled water instead of the alkali Let stand again overnight in refrigerator The pregnanediol is again collected by filtration and should now be colorless and entirely crystalline If not reprecipitate by again using 10 ml absolute alcohol and 30 ml distilled water Return to refrigerator overnight

The purified substance, after being in the refrigerator overnight, is collected as before by filtration transferred with absolute ethanol to a tared 30 ml. beaker, dried in the oven at 90°, cooled and weighed A melting point should be done on each specimen M P range is 205° 238° C

Calculation

$$\text{Daily pregnanediol output in mgs} = \frac{\text{24 hr vol}}{\text{vol. used}} \times \text{preg in}$$

sample weighed × 1 47 (1 47 = average calculated loss for method)

Because the steroids produced by the adrenal cortex play an important part in phases of diabetes such as ketoacidosis and because diabetes is sometimes of adrenal origin, the techniques for urinary 17-ketosteroids and 17-hydroxysteroids are listed here

URINARY 17 KETOSTEROIDS

References

Klendshoj Feldstein Sprague J Clin. End & Met *13*, 922 (1953)
Drekter, Heislo, Scism, Stern, Pearson & McGarack. J Clin End & Met *12*, 55 (1952)

Reagents

Ethylene chloride (also called—ethylene dichloride, 1, 2—dichloroethane)
Methyl cellosolve (filtered)
1% solv m-dinitrobenzene in methyl cellosolve
4 0 N KOH in methanol
NaOH pellets

Standards

5-30 γ-dehydroiso-androstrone (dehydroepiandrostrone) per ml. of methanol (stock solu 50 γ/ml.)

Procedure

1 Pipette 10 ml urine from measured 24° specimens into numbered glass stoppered tubes (Also run a procedure blank substituting distilled H_2O for urine)
2 Add 3 ml conc HCl
3 Place tubes with stoppers on in boiling water bath for 10 *mins*
4 Cool in pan of tap water
5 Add 10 ml 1,2 dichloroethane (ethylene chloride)
6 Stopper and shake 15 mins on mechanical shaker
(Note To avoid leakage, tighten stoppers invert tubes to wet ground glass surface and retighten stoppers)
7 Centrifuge, without stoppers for 5 mins at setting of 25-30 (Type SB 1)
8 Suction off urine (upper layer) with a pipette attached to a water aspirator
(Note Remove as much urine as possible without sectioning off much of the extracting solvent A small amount of urine will remain)

9 Filter (Whatman #1 paper) into 50 ml pyrex bottle with T stopper (Filter paper removes much of the residual urine)
10 Add 20 pellets of NaOH
11 With stoppers on, shake 15 mins in mechanical shaker
12 Filter solvent through Whatman #1 filter paper into clean, dry tube
(Note The last 3 steps remove unwanted chromogens and any water remaining)
13. Pipette 2 ml of ethylene chloride extract into clean, dry tube
14 Evaporate to dryness in boiling water bath, with or without suction
15 To dry extract add 0 4 ml 1% m-dinitro benzene in methyl cellosolve (Be sure extract is dissolved)
16 Add 0 3 ml of 4 0 N KOH in methanol
17 Mix by shaking rack with tubes
18 [illegible]

Standards

Standards should be treated as above starting with step #14

URINARY 17-HYDROXYCORTICOIDS

References

Reddy, Jenkins & Thorn, Metabolism I, 511 (1952)
Reddy—personal communication 1953-1954
Forsham—Recent Progress in Hormone Research, Vol IX, 297 (1954)
Smith, R W, Jr., Mellinger, R C, & Patti, A A Modification of the Reddy Procedure for 17-Hydroxycorticoids in Urine *J Clin. Endocrine & Metab* *14*, 336 (1954)

Reagents

"Dilute" sulfuric acid—310 ml reagent grade sulfuric acid and 190 ml. dist H_2O
Color reagent—65 mg phenylhydrazine hydrochloride dissolved in 100 ml "dilute" sulfuric acid
Na_2SO_4 (solid)
Na_2CO_3 (anhydrous)
"50%" H_2SO_4—1 vol reagent grade H_2SO_4 & 1 vol. dist H_2O
Standard solutions of cortisone (Merck) in purified butanol (5-40 γ-cortisone per ml) (Stock solution should be 100γ/ml)
Purified butanol

Procedure

Extraction of urine specimens

1 Pipette 10 ml of urine from measured 24 hr specimens into numbered 25 ml glass stoppered tubes

2 Adjust urine to PH 1 with "50%" H_2SO_4 (usually 4 drops is sufficient) Check with indicator paper

(Note The Na+ glucuranide of the corticoids are not very soluble in butanol Between PH 2 5 and 3 5 the Na+ salts are presumably converted to the acid form which is much more soluble in butanol At PH 1 a higher blank reading is reportedly obtained than at PH 2 5 but PH 1 will be used until further notice because of the greater speed of preparing the sample A slight variation in PH to either side of 1 0 does not matter

3 *Add approximately* 5 g Na_2SO_4 *(saturate urine and excess)* (Note The Na_2SO_4 removes protein from the glucuranide and reduces the amount of water dissolved in the butanol)

4 Add 10 ml purified butanol

5 Stopper tubes and shake not less than 15 mins on mechanical shaker

(Note *Before tubes are stoppered wipe* Na SO, *off ground glass* surface Tighten ground glass stoppers invert tubes and retighten stopper—otherwise leakage may occur)

6 Centrifuge in the same tubes with stoppers out, for 15 minutes at a setting of 40 on the large (Type SB 1) centrifuge (5 minutes is usually sufficient, but some specimens do not separate satisfactorily in this time)

7 Remove to a clean, dry test tube the butanol layer with an eye dropper type pipette being careful not to remove any urine

8 Add approximately 2 5 g of anh. Na_2CO_3 to the butanol extract

(Note The Na_2CO_3 removes any water remaining in the butanol and supposedly removes some unwanted chromagens)

9 Shake vigorously by hand (breaking any lumps of Na_2CO_3) after closing the end of the tube with a thumb covered with para film

10 Allow Na_2CO_3 to settle

11 Centrifuge 5 minutes at a setting of 15 on the small (Type C) centrifuge

12 Pour off supernatant butanol extract

13 Pipette 1 ml butanol extract into each of 2 tubes or for duplicate colorimetry into each of 4 tubes

Colorimetry

1 Add 4 ml "dilute" H SO_4 to tubes containing 1 ml of
   (a) butanol extract of unknown *urines (urine blank)*
   (b) butanol solution of standards (standard blank)

(c) purified butanol (acid blank)

2 Add 4 ml color reagent to tubes containing 1 ml of

(d) butanol extract of unknown urines (urine)

(e) butanol solution of standards (standard)

(f) purified butanol (reagent blank)

3 Cover open ends of tubes with parafilm held in place with thumb and invert to mix

4 Leave parafilm coverings on and incubate in water bath at 60-63° C for 20 minutes (2 or 3 mins extra heating is all right, but not less than 20 mins)

5 Cool 5 mins in cold tap water

6 Read in Klett colorimeter with #42 filter using acid blank (c) as a blank adjusting the instrument to zero

Calculations (A or B)

A *Standard Curve*

1 Prepare a standard curve
corrected standard reading (Klett) vs micrograms *cortisone*
a corrected standard reading
standard—standard blank—reagent blank
(e-b f) = corrected standard reading

2 Obtain corrected unknown reading
urine—urine blank—reagent blank
(d a f) = corrected unknown reading

3 Read corrected unknown concentration in γ/ml off standard curve

4 Multiply value obtained in (3) by urine vol in ml

B Direct comparison with standard

1 Obtain corrected standard reading and corrected unknown reading as in A

2 Divide corrected unknown reading by corrected standard reading, multiply by concentration of standard, multiply by the vol. of the urine specimen in ml

$\frac{(d\ a\ f)}{(e\text{-}b\text{-}f)}$ × conc of std × ml urine = total corticoid content of the specimen

PREPARATION OF BUTANOL FOR CORTICOID DETERMINATION

1 To a bottle of n Butyl Alcohol, "Baker Analyzed" Reagent, add approximately 100 ml phenylhydrazine-H_2SO_4 reagent per liter of butanol

(Note A second bottle of butanol should be treated with phenylhydrazine-H_2SO_4 as soon as the first is empty)

2 Allow to stand at least 1 week (longer time is all right)

3 Wash the treated butanol with one half its volume of saturated aqueous solution of Na_2SO_4
(Note The water removes part of the phenylhydrazine H_2SO_4 and the Na_2SO_4 aids in preventing water from dissolving in the butanol)
4 Separate the butanol from the water (1 liter separatory funnel)
5 D [illegible]
([illegible]
b [illegible]
necessary to obtain butanol of the desired purity from 3 or more to 2)

a Collect all fractions boiling at 100° C or less in a clean bottle (Bottle A) This fraction contains water saturated butanol plus an excess of water

b Collect all fractions boiling above 100° and below 120° C in a second bottle (Bottle B)
(Note This fraction should contain very little water and should be collected separate from (a), otherwise, the butanol will reabsorb the excess water The reason for not attempting to obtain the 117°-118° fraction at this point is mainly empirical—we have never been able to get a color reagent blank of less than 15 Klett units with the material obtained in this step)

c Discard brown material left in distilling flask

d Clean and dry distilling apparatus

e Redistill material in Bottle B

(1) Collect fractions boiling at or below 100° C in Bottle A

(2) Collect fractions boiling above 100° C and below 117° C in Bottle B

(3) In a clean bottle (Bottle C) collect material boiling at 117° to 118° C (*Purified Butanol*)

(a) Run a H_2SO_4 blank and a color reagent blank on this material

(b) If, using the acid blank as zero, a reading of 3 Klett units or less is obtained with the reagent blank, the material is satisfactory and may be transferred to a permanent reagent bottle (Bottle D)

(c) If a reading greater than 3 is obtained, pour the material back into Bottle B

f After removal of the water with the aid of a separatory funnel the butanol in Bottle A can be redistilled as is the material in Bottle B

Because serum chorionic gonadotrophin determinations are used as a gauge of estrogen deficiency in diabetic pregnancies and as a guide for estrogen therapy, serum deter-

minations for chorionic gonadotrophin are included and are as follows:

1. Draw about 6 ml venous blood
2. Transfer to clean dry test tube
3. Let stand till clot forms
4. Remove clot
5. Centrifuge at setting of 25 for 5 minutes
6. Decant serum into clean dry test tube
7. Label tubes as to name, date and number of rat units to be tested (Note. Serum can be kept in cold room if it is not to be utilized immediately)
8. To each of two centrifuge tubes per specimen add approximately 10 ml of 95% ethyl alcohol
9. Label centrifuge tubes (name, date and total amount of serum)
10. Pipette the same amount of serum from each sample into each of the duplicate tubes (0.5 ml per tube to scan for 200 rat units/100 ml serum the dilution usually used)
11. Shake immediately to suspend evenly—placing end of thumb over the tube
12. Place in cold room overnight (8-16 hrs refrigeration needed)
13. Centrifuge at setting of 25 for 5 minutes to pack precipitate
14. Pour supernatant alcohol into waste alcohol bottle
15. Drain, leaving tubes inverted for 5 minutes in rack on towel
16. Add approximately 5 ml. ether and stir with stirring rod till precipitate is well mixed (Note. Ether removes estrogens)
17. Withdraw stirring rods and place on clean towel (Note Keep tubes and stirring rods in the same order, as the stirring rods are to be used again in the same tubes)
18. Centrifuge at setting of 25 for 5 minutes
19. Pour ether into waste ether bottle
20. Drain tubes for about one minute
21. Add 1 ml of physiological saline
22. Stir with stirring rods
23. Place in water bath at approximately 50° C, no warmer, for 5-10 minutes, with rods still in tubes. (Note This is to drive off residual ether, b p 35° C)
24. Agitate occasionally while heating
25. Add 5 ml physiological saline (total vol. 6 ml/tube and remove stirring rods
26. Inject 1 ml of the saline suspension twice daily for 3 days (total—6 ml. per rat) into female rat (21 days old) (Note The injections should be at least 4 hours apart. The rats should be injected subcutaneously at the back of the neck)
27. Read the test on the third day after the final injection. (Example Inject Wed, Thur., Fri—read test Mon.)

Reading the Test

1 Positive test is the presence of corpus luteum in the rat. Corpus luteum of rat is *red* not yellow
2 The corpus luteum may be distinguished from a hemorrhagic area by poking it with forceps The hemorrhagic area breaks easily, but the corpus luteum is rather tough and has a sort of rubbery consistency
(Note An instructor is almost indispensable at this point unless you have observed rat corpora lutea before)
3 If 0 5 ml serum is used a positive test indicates 200 or more rat units of chorionic gonadotrophin per 100 ml. serum A negative test, less than 200 rat units per 100 ml serum

ml serum used	Positive test (R U /100 ml. serum)
0 5	200 or more
0 3	333 or more
0 2	500 or more
0 15	666 or more
0 1	1000 or more
0 05	2000 or more

INDEX

SECTION 1

Basic Principles

THE ubiquity of diabetes necessitates a reasonable familiarity with its management, not only by the physician particularly interested in metabolic conditions, but also by the surgeon, by workers in other special fields, and particularly by the general practitioner

The imperative need for Insulin by every patient with severe diabetes and by practically all diabetic children is now generally recognized The safe, economic, and rational use of Insulin depends upon the establishment of an equilibrium between food requirements and the dose of Insulin, and this mode of treatment rests squarely upon fundamental and simple dietetic principles

Furthermore, it is desirable that every patient with diabetes, whether mild or severe, have sufficient knowledge of the benefits of Insulin that he may, through instructions given by his physician, recognize without delay the urgent necessity for its use should his carbohydrate tolerance suddenly become further impaired by infection, surgery, trauma, or other factors "Other things being equal," one authority states, "the diabetic who knows the most lives the longest "

DEFINITION OF DIABETES

Diabetes mellitus is a hereditary disease characterized by impairment of the body's normal ability to metabolize or utilize food This defect is manifested by increased amounts of sugar in the blood and subsequently by the excretion of sugar into the urine The abnormality is largely dependent upon an actual or relative deficiency of insulin resulting from a disturbance in the function of the islands of Langerhans of the pancreas or interference with the action of insulin in the tissues, it involves faulty storage of sugar in the liver, the overproduction of sugar in the liver, and possibly a diminished utilization of sugar by the tissues Insulin not only promotes normal combustion of dextrose in the tissues, but influences the metabolism of protein and fat

PHYSIOLOGY OF NORMAL AND DIABETIC METABOLISM

A thorough acquaintance with the physiological principles underlying normal metabolism is a prerequisite to understanding the derangements characteristic of

manner that toxic by products (ketones) are found in large quantities in the liver and produce ketosis (the diabetic type of acidosis) and finally diabetic coma

Carbohydrate—The far reaching importance of carbohydrate metabolism is apparent from the fact that dextrose is the primary sugar into which carbohydrates are converted before they can be utilized by the animal body Dextrose is the most readily available source of energy for the body and in the diet normally supplies approximately forty percent of the total energy required The different steps involved in the transformation of dextrose into glycogen and its storage in the liver are complex but the decreased deposition of glycogen from glucose under the influence of Insulin is the most firmly established physiological action of the hormone Muscle glycogen is not directly a source of blood sugar although it may serve the purpose indirectly through its conversion into lactic acid which can be utilized by the liver as a source of hepatic glycogen

zymes which in turn are activated by their coenzymes The steps from glycogen to pyruvic acid can occur in the absence of oxygen If there is an impairment in oxygen supply or an excessively rapid rate of glycogen breakdown pyruvic acid tends to accumulate and is rapidly converted to lactic acid which again may be converted to glycogen by the liver (see Vitamins page 74)

Protein—Protein is characterized by its content of nitrogen It usually contains sulfur and sometimes phosphorus Its units are amino acids and these building stones represent the end products of protein digestion which may be reassembled by the body to provide new forms of protein essential to the animal The incombustible amino (NH_2) group is removed by the liver and then excreted as urea whereas the carbohydrate remainder may be oxidized to produce energy In this manner about 58 percent of the protein in the body may become available to the organism as sugar Protein also exerts a stimulatory effect upon metabolism a specific dynamic action which makes the use of too large quantities of this foodstuff undesirable especially in diabetes Approximately 15 percent of the total calories are supplied by dietary protein

Fat—Fat is a more concentrated source of energy than either carbohydrate or protein and yields about twice as many calories per gram Consequently fat can be employed *to increase the caloric value of a diet without substantially increasing its*

diabetes. Although recognized for centuries, only in the last thirty years has the true nature of the disease become known. Diabetes affects profoundly all the chemical interchanges taking place in the body cells as they deal with the various energy-supplying foodstuffs necessary for their existence, and although the disease is primarily a disturbance of carbohydrate metabolism, other systems are affected as well.

FUNCTION OF FOOD IN HEALTH

Man's body, like an engine, requires fuel, or energy, which must be derived from his food. The essential elements of food which furnish energy and heat are carbohydrate, protein, and fat (Table I). Water, mineral salts, and vitamins are just as *indispensable for the maintenance of normal nutrition, but they* do not enter directly into the energy exchanges of the body. The carbohydrate portion of the diet is taken in the form of starch, such as potatoes and other vegetables, bread, pastry, macaroni, and sugar. The sources of protein are largely lean meat and eggs, and fat is supplied in butter, cream, salad oil, and fat meat. Many foods contain all three classes of foodstuffs, but there is usually a preponderance of one which serves as a basis for classification. Although all supply energy and serve to "heat and run the body," each one behaves in a more or less characteristic manner and has its

TABLE I • *Normal Daily Requirements*

ENERGY PRODUCING FOODS (25 to 70 cal. per kg.)*	(a) CARBOHYDRATES (200 to 400 Gm.) (40%)	*Glucose is the fuel of life.* The diet must supply enough to maintain normal stores in liver and muscle. Carbohydrate provides glycogen to protect the liver
	(b) PROTEINS (1 to 3 Gm. per kg.)* (15%)	Provide enough to maintain nitrogen balance and permit normal growth and *repair of tissues.* Average 1 Gm. per kg. of body weight (adult)
	(c) FATS (60 to 125 Gm.) (45%)	Fats serve primarily as reserve and secondarily as *available fuel.* The optimum requirement has not been definitely determined. The normal daily requirement is about 100 Gm.

*High values for young, active persons. Low values for old, sedentary patients.

own peculiar functions. For example, carbohydrate is especially useful because it so promptly supplies energy for muscular work and since, in addition, its oxidation exerts some regulatory effect upon the metabolism of fat. Thus, impaired consumption of carbohydrate, as in diabetes, deranges fat metabolism in such a

level in the liver itself When the rate of ketogenesis in the liver exceeds the rate of oxidation of ketones in the tissues ketonemia and ketonuria ensue and the excess is excreted in the urine as acetone and diacetic acid Thus ketogenesis indicates either a relative or absolute shortage of carbohydrate for fuel

Some of the ketones are excreted as free acid other portions are neutralized by increased ammonia production and by the buffer action of the blood by which carbon dioxide is displaced from the bicarbonate of the plasma Fixed base chiefly sodium is lost when the ketosis is severe and dehydration and hemoconcentration occur Compensatory mechanisms are overwhelmed and several outstanding alterations from normal gradually appear (1) The carbon dioxide combining power of the blood is reduced in proportion to the severity of the acidosis (2) continued loss of fixed base accentuated by vomiting entails a reduction in sodium chloride and electrolyte concentration lowered alkali reserve diuresis and dehydration (3) acetone and diacetic acid appear in the urine in large quantities (4) hemoconcentration develops (5) the *p*H of the blood shifts toward the acid side (6) Kussmaul breathing (air hunger) ensues and the blood pressure falls followed by circulatory collapse depression of renal activity retention of nonprotein nitrogen in the blood subnormal temperature and finally death

INCIDENCE OF DIABETES

It seems probable from recent data that there are more than 2 000 000 cases of diabetes in the United States today Statistical reports have pointed out the increasing frequency of the disease Joslin has estimated that there are 2,500 000 persons living in the United States today who either have or will develop diabetes Reports and surveys concerning the incidence of diabetes mellitus in other countries are not as yet available

An analysis of the incidence of diabetes in over 45 000 Army selectees shows that the disease is three to four times as prevalent among young adults as has hitherto been assumed on the basis of earlier studies It has been predicted that if mortality rates continue to follow the same trend as at present in the United States by 1980 deaths from diabetes will be exceeded only by those from heart disease

Part of the increasing incidence of diabetes is merely apparent and is due to the general application of improved methods of case finding and treatment There actually are more cases however a fact which is partially explained by increased longevity of the population as a whole Diabetes is most frequently found in women past middle life although no age is exempt

FACTORS CONCERNED IN THE CAUSATION OF DIABETES

The immediate cause of diabetes mellitus is a deficiency of endogenous insulin Whether the blood-sugar-reducing principle elaborated by the pancreas of the diabetic is quantitatively or qualitatively deficient, or whether it is normal as originally produced but subsequently neutralized by other agents, the end result is insulin deficiency and diabetes Besides this immediate cause, however, there are certain predisposing factors

HEREDITY

A predisposition to diabetes seems to be inherited as a Mendelian recessive characteristic this influence is now considered to be of primary importance, although such predisposition may not be revealed until late in life or even until long after the development of the disease It has been estimated that approximately one out of every four persons is a "diabetes carrier" (Figure 2A) In view of these facts, it is inadvisable for members of diabetic families to intermarry, because of the greatly increased probability that such intermarriages may produce diabetic offspring

OBESITY

How obesity predisposes to diabetes has not been explained, but the fact remains (Figure 2B) It has been stated that diabetes is the penalty of obesity and that the greater the obesity, the more likely is nature to enforce the penalty Obesity and overeating are usually associated but overeating alone probably does not lead to diabetes It is well known that insulin, whether endogenous or exogenous, increases the appetite Possibly people overeat because their islands of Langerhans are initially overactive, eventually this overaction gives rise to exhaustion, and then too little, rather than too much, insulin is produced An increased incidence of diabetes parallels somewhat an improvement in the economic status of individuals or nations Apparently two causative forces operate to disturb the metabolic equilibrium of large masses of people under such circumstances More food material is taken in, and less muscular energy is expended to burn it up

Newburgh has shown that glucose tolerance tests may be returned to normal in more than three-fourths of those adult obese hyperglycemic patients who undergo adequate reduction of weight

ENDOCRINE FACTORS

It has long been observed that overweight predisposes to diabetes in the adult, although overheight is a frequent forerunner of diabetes in the child Such observations point to an endocrine factor, probably the pituitary gland The epochal work

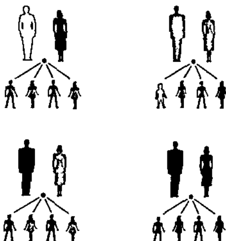
THE ULTIMATE CAUSE OF DIABETES IS UNKNOWN

HEREDITY AND OBESITY CONTRIBUTE TO ITS ONSET . . .

FIGURE 2A

Heredity

The Mendelian type of heredity is a background for diabetes. Diabetes depends upon inheritance of a diabetic trait plus the effect of one or more secondary factors



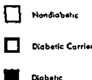
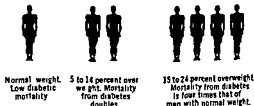


FIGURE 2B

Obesity

Diabetes is a penalty of obesity. Of 1 000 diabetics examined 770 were overweight.
The mortality rate from diabetes in men past age 45 increases with the degree of obesity





26 percent overweight. Mortality from diabetes is ten times that of men with normal weight.

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of Houssay and others has finally proved a close interrelationship between this gland and carbohydrate metabolism More recently, the influence of the pituitary has been emphasized by the work of Young, who produced permanent diabetes in dogs by injecting anterior pituitary extracts Further investigations, confirmed by Best, revealed that the islet cells of the pancreas in these animals had been severely damaged and the actual insulin content of the islet tissue was extremely low The Toronto school and Lukens and Dohan and others have now demonstrated that islet-cell damage may be prevented or reversed by starvation or fat feeding and by controlling *active* diabetes by means of proper dietary measures in conjunction with exogenous Insulin More recent observations prove that hyperglycemia per se is the factor responsible for progressive islet damage The implications of this discovery are far-reaching, especially since the experimental pituitary diabetes of animals has actually been cured by controlling the blood-sugar level

The recent demonstration by Conn that the diabetic syndrome could be induced in normal men by administration of adrenocorticotropic hormone emphasizes still further the importance of the pituitary-adrenal relationship

The adrenals—and thyroid—are in close relationship with the pancreas Efforts have been made to treat diabetes from the endocrine standpoint, with results which are inconclusive except in those cases resulting from surgically accessible adrenal tumors The adverse influence of hyperthyroidism upon diabetes is undoubted, and complicating factors of this type must be carefully considered when therapy is instituted

MISCELLANEOUS FACTORS

Other factors which sometimes seem to be responsible for the development of diabetes but probably are rarely if ever causative, are infection, particularly of the gall-bladder region, disease resulting in injury to certain areas of the midbrain, and occasionally arteriosclerosis Traumatic diabetes is probably nonexistent unless there is avulsion or destruction of the major portion of the pancreas

Although diabetes is seen most frequently in patients past middle life, no age is exempt and females are more commonly affected than males The incidence of the disease is greater among Hebrews than among Gentiles It is also greater among Negroes than was formerly suspected Studies of the Indians of Arizona, U S A, and inmates of institutions by Joslin emphasize the universality of diabetes The number of cases in any population is almost directly proportional to the search made for them It is said that diabetes among the Chinese and Japanese is not only infrequent but relatively mild The food of these peoples is largely carbohydrate, and their apparent relative freedom from diabetes suggests the possibility that a large proportion of carbohydrate in the diet is not the cause of the disease and per-

haps may even indicate the type of diet which is most suitable in its management Himsworth observed that the diets of persons who developed diabetes were higher in fat and lower in carbohydrate than those of normal people

PREVENTION OF DIABETES

Because of the etiological significance of obesity, the prophylactic value of avoiding overnutrition must be emphasized By urging the relatives of the diabetic to keep their weight within normal limits, the development of diabetes in those most susceptible to it might be prevented When diabetes or diabetic heredity exists, further transmission of the disease may be completely blocked only if the chosen partner in marriage is a nondiabetic member of a nondiabetic family (see Figure 2A)

If the conclusions drawn from experiments on animals may be applied to human diabetes early diagnosis and efficient control of the active symptoms (hyperglycemia) may be expected to prevent further development of the defect

SYMPTOMS AND SIGNS OF DIABETES

The date of onset of diabetes is usually indefinite and its approach insidious The most characteristic symptoms of the disease are the passage of large amounts of urine, increased thirst, and excessive appetite, accompanied by loss of weight and strength The first symptom noticed by the patient is usually polyuria, since, in order for the kidney to dilute and eliminate the excess amount of sugar brought to it through the blood stream, large amounts of water must be abstracted from the tissues and passed as urine This same mechanism explains the next commonly encountered symptom, namely, polydipsia (excessive thirst) Loss of strength develops because the patient is deprived of the food value of the sugar lost in the urine and because the utilization of fat is imperfect as well Although the blood of the untreated diabetic may contain abnormally large quantities of sugar and fat, these substances cannot be properly utilized, so the patient literally starves amidst an abundance of food Thus polyphagia (excessive hunger) appears Other commonly encountered complaints are skin disturbances, such as localized or generalized pruritus, furuncles, carbuncles, and slowly healing ulcers, disturbances of vision, numbness and tingling, and pain (neuritis), especially in the lower limbs

The patient s urine contains sugar and usually has a high specific gravity Diacetic acid may also be present, indicating that acidosis exists Examination of the blood discloses a sugar content above normal, especially after meals

In mild cases, or soon after the actual onset of the diabetic state, glycosuria may exist without subjective symptoms and not infrequently it is the only early sign Such instances represent a diagnostic problem which demands sufficient study